Chemical Name: 4-Nitrophenol
CASRN: 100-02-7
Submitter: Solutia

As the Agency received data from High Production Challenge Program participants, it posted notice of and links to those data here for public review and comment. Companies and consortia were requested to defer any proposed new testing on their chemicals for a period of 120 days from when their Test Plans and Robust Summaries were posted to the Internet, in order to allow for technical public comment regarding the possible provision of additional existing data or other technical information which might address or eliminate the need for some new testing.

Some sponsors of chemicals submitted revised test plans and robust summaries to the Agency and referred to them as "final" submissions. EPA previously referred to the most recent submission as "revised" and has made no distinction or judgment whether a submission is final. Lastly, technical public comments on test plans and robust summaries were also provided for several chemicals/categories.

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The pdf contains the following documents:

201-14390

NCIC HPV
Sent by: Mary-Beth Weaver

04/09/2003 09:35 AM

To: NCIC HPV@EPA, Peter Wendolkowski/DC/USEPA/US@EPA
cc: Mary-Beth Weaver/DC/USEPA/US@EPA, Ralph Northrop/DC/USEPA/US@EPA, Vanessa Williams/DC/USEPA/US@EPA
cc: Mary-Beth Weaver/DC/USEPA/US@EPA, Ralph Northrop/DC/USEPA/US@EPA, Vanessa Williams/DC/USEPA/US@EPA
Subject: HPV Submission: 4-Nitrophenol

"Johannsen, Frederick R" <frjoha@solutia.com> on 10/31/2002 05:07:50 PM

To: Rtk Chem/DC/USEPA/US@EPA
cc:
Subject: HPV Submission: 4-Nitrophenol

Please see attached submission

<<HPVPNPtrans.doc>> <<HPV FinalP-NITROPHENOL.doc>>
<<pnp.rtf>>

- HPVPNPtrans.doc
- HPV FinalP-NITROPHENOL.doc
- pnp.rtf

Solutia Inc.
575 Maryville Centre Drive
St. Louis, MO 63141

P.O. Box 66760
St. Louis, MO 63166-6760

October 31, 2002

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

In re: HPV Challenge Program
AR-201
4-Nitrophenol
CAS Number 100-02-7

Solutia, Inc., Company Registration Number , is pleased to submit the attached Test Plan and Robust Summaries for 4-nitrophenol (CAS Number 100-02-7) as a part of our commitment to the EPA High Production Volume Challenge Program (AR-201).

The attached files are:

1. This cover letter in MS Word 2000
2. Test Plan in MS Word 2000
3. Robust Summaries (IUCLID format) in MS Word 2000

The complete matrix of SIDS data elements, including physical/chemical properties and results of biological and toxicology studies, indicate that no additional testing is required.

Please contact me at 314-674-8815 if there are any questions relating to this submission.

Sincerely,

Frederick R. Johannsen

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

4-NITROPHENOL

CAS NO. 100-02-7

Prepared by:

Solutia, Inc. Registration No.

575 Maryville Centre Drive,
St. Louis, Missouri 63141

EXECUTIVE SUMMARY

Solutia Inc. voluntarily submits the following screening information data and Test Plan covering the chemical, 4-Nitrophenol, also known as para-Nitrophenol or PNP (CAS No. 100-02-7), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with PNP. Use of key studies or estimation models available from data already developed provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing.

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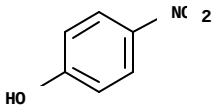
TEST PLAN FOR P-NITROPHENOL (PNP)

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Phenol, 4-nitro-, or PNP. The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of PNP, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature and fulfills Solutia's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of PNP and associated nomenclature.



Phenol, 4-nitro-

CAS No. 100-02-7
Synonyms: 4-Hydroxynitrobenzene; p-Nitrophenol; para-nitrophenol; PNP

B. Manufacturing & Use

PNP is manufactured by a single US producer, Solutia Inc., at a single manufacturing site. The manufacturing operation is a closed, continuous process. Only a few employees are involved in its manufacture and have minimal potential for skin or airborne exposure, which occur chiefly during material transfer operations. Due to the high acute hazards associated with its potential to cause methemoglobinemia, specific manufacturing procedures and practices have been established to minimize the exposure potential to PNP.

p-Nitrophenol is sold to a limited number of customers at a few US processing sites and exported to ex-US sites for the express purpose of full chemical conversion into other

industrial chemicals. As such, PNP is expected to chemically react to form chemicals used as dyes/pigments, pharmaceuticals, analgesics and adhesives. There are no known or suspected consumer exposures to PNP resulting from TSCA-related activities, as PNP is consumed as a chemical intermediate. Loss to the atmosphere or from non-POTW aqueous streams during manufacturing or processing is minimal. Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This initial assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with PNP. The data used to support this program include those Endpoints identified by the US EPA (1998a); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3.Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – This designation not used in this Dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. Additional studies have been identified during our literature search on the referenced HPV endpoints but have not been summarized in this Dossier. The reader is referred to three additional data compendia which also summarize available data on the physical-chemical properties, ecotoxicity, environmental fate and health effects of p-nitrophenol. These include the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000), the ECB IUCLID Dossier for p-Nitrophenol (2002), and the Hazardous Substances Data Bank (HSDB) (2002) for p-Nitrophenol.

II. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Hence, no further testing for any of the HPV Endpoints is deemed necessary (Table 1).

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from reputable references and cited as an Accepted or Peer Reviewed value in the PNP Hazardous Substances Data Bank (2002) and/or IPCS CICAD on Mononitrophenols (2000). These endpoints have been classified as "2-Reliable with restrictions".

Environmental Fate values for Transport (Fugacity) were obtained using a computer estimation –modeling program (EPIWIN, 2002) recommended by EPA; they have been classified as "2-Reliable with restrictions". Biodegradation data were summarized in a published article reporting results of multiple studies following OECD # 301/GLP guidance and thus classified as "1-Reliable without restriction". Photodegradation data was obtained from a published study following EPA test guidelines and was considered "2-Reliable with restrictions". In keeping with OECD SIDS guidance, no testing for Stability in Water is planned with PNP as it is generally recognized as "stable" in aqueous solutions.

Ecotoxicity Endpoints were met with studies that were conducted according to OECD guidelines for Acute Invertebrate Toxicity (OECD 202) and Acute Plant Toxicity (OECD 201), or conducted according to study design and test parameters which preceded, but were consistent with OECD test guidance (Acute Fish Toxicity-OECD # 203). Studies supporting the Acute Invertebrate and Acute Plant Endpoints were designated a reliability level of "1-Reliable without restriction", while the Acute Fish study was designated "2-Reliable with restrictions", as it was well documented but conducted prior to inception of GLPs.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing, and Reproductive Toxicity) have all been filled by way of tests which either conformed directly with OECD test guidance or followed test designs similar to OECD guidance. The Acute Toxicity Endpoint was supported by a study which followed OECD guideline 401 and GLPs and was considered "1- Reliable without restriction". The Repeated Dose Toxicity Endpoint was met with an OECD guideline 408 study conducted in accordance with GLPs. It also was codified as "1- Reliable without restriction". Both the Ames test as well as an *in vitro* Chromosomal Aberration assay, used to support their respective Endpoints, were conducted by the US National Toxicology Program (NTP). The Ames test followed a study design equivalent to OECD guideline # 471 while the cytogenetics study was similar to, but not identical with, OECD guideline # 473. Thus, the Ames test was categorized as "1- Reliable without restriction" while the cytogenetics study was classified as "2- Reliable with restrictions".

A 2-Generation Reproduction Study fulfills the HPV requirements for the last Mammalian Toxicity Endpoint. This study was conducted to meet US EPA pesticide guidance for reproductive toxicity both in design and GLP compliance. While it deviated slightly from OECD guideline # 416, it has been classified as "1- Reliable without restriction" since it has been accepted by EPA to fulfill the Reproductive Toxicity data requirement for reregistration purposes.

Following is a tabular depiction of data availability and testing recommendations for p-Nitrophenol (PNP).

Table 1. Test Plan Matrix for para-Nitrophenol

	Info. Avail.?	OECD?	GLP?	Other Study?	Estimat. Method?	Accept-Able ?	Testing Recomm.?
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	Y	-	Y	N
Boiling Point	Y	R	N	Y	-	Y	N
Vapor Pressure	Y	R	N	Y	-	Y	N
Partition Coefficient	Y	R	N	Y	-	Y	N
Water Solubility	Y	R	N	Y	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	L	Y	-	Y	N
Stability in Water	Y	N	N	N	-	Y	N
Biodegradation	Y	Y	L	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	Y	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	N	Y	-	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	L	Y	-	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	L	Y	-	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	Y	Y	Y	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	N	Y	Y	-	Y	N
Reproductive Toxicity	Y	N	Y	N	-	Y	N

Y = Yes; N = No; L = Likely, but not specified; R = Reputable Reference;
- = Not applicable

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of para-Nitrophenol (PNP)

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 20 ^{o}C)	Water Solubility (mg/L)	Partition Coefficient (Log Kow)
p-Nitrophenol CAS No. 100-02-7	> 279	114	0.0067	16,000 @ 25 ^{o}C.	1.91

All HPV Endpoints for Chemical/Physical Properties have been completed with reliable information and taken from either primary or reputable textbook references (Table 2). The values, which are included in the Robust Summary section of this Dossier, have been internationally accepted as accurately depicting the properties of PNP and are cited in the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000) and/or cited as peer-reviewed references in the Hazardous Substances Data Bank (HSDB, 2002). They have been classified as "2-Reliable with restrictions". Additional Chemical/Physical property values can also be found in the IPCS CICAD No. 20 (2000) and the ECB IUCLID Dossier for P-Nitrophenol (2002).

In summary, these data indicate that PNP is a solid at room temperature and has a low vapor pressure. It has a low octanol:water partition coefficient and is soluble in water.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

Extensive reviews and study citations in the Environmental studies area have been published on PNP, and are summarized in the IPCS CICAD (2000), in the HSDB (2002) and in the ECB IUCLID Dossier (2002) for PNP. Key studies have been selected for this

Dossier, which fairly depict the consensus conclusion/values for each of the HPV Endpoints listed (Table 3), and are summarized in the Robust Summary section of this Dossier. A comparative assessment of PNP Biodegradability employing 5 OECD Guideline 301 methods fulfills this HPV Endpoint; it has been designated as "1-Reliable without restriction". The molecular structure of PNP possesses only 2 functional groups (aromatic nitro and phenol), both of which are listed as types of Organic Functional Groups that are Generally Resistant to Hydrolysis (Table 7.1, Lyman et al, 1990). PNP is also considered "stable" in water by the German Umweltbundesamt, based on tests conducted in Germany (Schmidt-Bleek et al, 1982). PNP hydrolysis has also been reported as "nil" at pH 2, pH 7 and pH 12 (Capel and Larson, 1995). Photochemical degradation of PNP in an aquatic system has been evaluated in "the EPA Test" using the methodology of Leifer and Stern (Hustert et al, 1981). Estimation of Transport (Fugacity) was made using an EPA-accepted estimation model (EPIWIN, 2002). These values have been designated as "2-Reliable with restrictions". An overview of the known qualities of the environmental properties of PNP is provided below.

The Environmental Fate of PNP can be summarized, as follows. Upon release to the air, PNP would be expected to exist in a vapor state, based on its vapor pressure and would be degraded in the atmosphere by reaction with photo chemically-produced hydroxyl radicals; the half-life for this reaction in air is approximately 6 days (Table 3 - Photodegradation). However, PNP is extensively adsorbed to particles, in both the air and soil. Thus, as PNP is mostly particle-bound, its availability for photochemical reactions is limited (IPCS, 2000). Significant volatilization from soil or water to air is not expected, based on its Vapor Pressure (Table 2) and Henry's Law constant, respectively (IPCS, 2000). Atmospheric PNP, bound to particles, is expected to wash out to surface waters and soils by dry and wet deposition. Fugacity modeling (Table 3) indicates virtually complete allocation to water and soil; essentially no allocation was made to air or sediment (Table 3 - Fugacity). In aqueous solution, PNP appears stable (Table 3-Stability in Water). PNP has been classified as possessing low to moderate potential for soil sorption and can be decomposed under aerobic conditions, thus being classified as "Inherently Biodegradable" (IPCS, 2000)(Biodegradation – Table 3). Microbial decomposition can occur in different environmental compartments after adaptation of the microflora. Further biotic degradation under anaerobic conditions also occurs following extended acclimatization of microbial communities (Table 3 - Biodegradation). Measured values (IPCS, 2000; ECB IUCLID, 2002) indicate PNP has a low potential for bioaccumulation in aquatic species.

Table 3. Environmental Fate and Biodegradation Parameters for para-Nitrophenol (PNP)

Chemical	Biodegradation Rate	Stability in Water	Fugacity (%)	Photodegrad. Rate (T ½)
p-Nitrophenol CAS No. 100-02-7	~ 90 %	Stable	Air – 4.98 Water – 36.3 Soil – 58.7 Sediment – 0.02	5.7 (pH 5) 6.7 (pH 7) 13.7 (pH 9) .

Conclusion – Adequate studies following either OECD or EPA test guidance are available to provide needed information regarding the Biodegradation and Photodegradation of PNP. Information on Transport (Fugacity) were completed using EPIWIN, an accepted estimation-modeling program. As PNP possesses only functional groups generally known to be resistant to hydrolysis, testing for stability in water is not needed (SIDS Manual-new draft version). Therefore, no additional data development is warranted for these HPV Endpoints.

C. Aquatic Toxicity

The aquatic toxicity of PNP has been extensively reviewed (IPCS, 2000; HSDB, 2002; ECB IUCLID, 2002) and contains both acute and chronic toxicity studies on algae, invertebrates and fish. Studies selected for development of Robust Summaries are reported in Table 4 and depict the level of toxicity generally observed for these Endpoints within the overall dataset.

Both the Acute Invertebrate and the Acute Algae studies were conducted according to OECD test guidance # 202 and 201, respectively. While no mention was made of GLP compliance in the referenced publications, it is reasonable to assume both were conducted under GLP auspices as they followed OECD method guidance and were conducted to meet national regulatory mandates. Thus, both studies are considered "1-Reliable without restriction". The Acute Fish Toxicity study was conducted prior to inception of OECD/GLP guidance but is considered well documented and used methodology consistent with OECD guidance for this study type. This study is considered "2- Reliable with restrictions" only because it was conducted prior to codification of testing and GLP guidelines.

Table 4. Aquatic toxicity parameters for para-Nitrophenol (PNP)

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
p-Nitrophenol CAS No. 100-02-7	5.8 (bluegill-96 hr)	22.0 (Daphnia-48 hr)	32.0 (96-hrs)

PNP is considered to be "Slightly Toxic" toward these and other aquatic species following acute testing (IPCS, 2000). Based on the pattern and release scenarios envisioned, PNP is expected to present a negligible risk to aquatic organisms.

Conclusion – Adequate studies which meet internationally accepted test guidelines are available on all 3 Aquatic Toxicity Endpoints to assess the acute aquatic toxic hazards associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

Table 5. Mammalian Toxicity of p-Nitrophenol (PNP)

Chemical Name/ CAS no.	Acute Toxicity		Repeat Dose Toxicity			Reprotoxicity	Mutagenicity –In Vitro	
	OLD50 (rat)	DLD50 (rabbit)	90-day	28-day	Chronic	2-Gen.	Ames	Chrom. Aberr.
p-Nitro-phenol 100-02-7	230 mg/kg	> 5000 mg/kg	(oral-rat) NOEL 25 mg/kg/d	(inhal-rat) NOEL 5 mg/m3	(dermal-mouse) NOEL (systemic tox./carcin.) 160 mg/kg/d	(dermal-rat) NOEL (maternal-systemic) 250 mg/kg/d NOEL (reprotox) 250 mg/kg/d	Neg.- All strains +/- S9	Neg. (- S9) Pos. (+S9)

1.0 Acute Toxicity

Results of acute toxicity studies by both the oral and dermal routes of exposure have been conducted as summarized in Table 5. Both studies were conducted using study designs consistent with OECD Test Guidelines 401 and 402, respectively, under auspices of GLPs, and are deemed "1- Reliable without restriction". The acute rat oral toxicity study has been chosen as the key study to fulfill this HPV Endpoint. The acute rabbit dermal toxicity study is included as Supplemental information.

PNP is considered to be moderately toxic after acute oral exposure to rats. As there were no deaths or untoward signs of toxicity after acute dermal exposure well above generally accepted Limit Dose levels (1,000 mg/kg), PNP is considered practically non-toxic after acute dermal exposure to rabbits. However, based on the ability of PNP to produce methemoglobinemia in humans, this material is considered to be toxic in the workplace by all acute exposure routes. Additional acute toxicity values in animals can be found listed in the three compendium reports cited above.

Conclusion – A quality study, compliant with OECD/GLP guidance, is available to assess the Acute hazards associated with PNP. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

PNP has been adequately tested by several routes of exposure to define its Repeated Dose Toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route. This study was conducted using a study design consistent with OECD Test Guideline 408, and under GLP auspices and is considered "1- Reliable without restriction". Early deaths related to PNP acute toxicity, and exacerbated by repeat dosing, occurred at dosage levels of 70 and 140 mg/kg/d. No other treatment-specific effects or organ pathology, including lack of involvement of male and female gonads (i.e. testes and ovaries), were affected. A NOEL of 25 mg/kg/d was established. A summary of this study and a 4-week Range Find study are found in the Robust Summary section of this Dossier. The IPCS CICAD (2000) also summarizes a 28-day oral gavage study (Andrae et al. 1981) with PNP at substantively higher levels, which resulted in excessive toxicity. This study was not considered in this review as it is not available in English and is superceded by the current study, which is of a longer exposure duration by the same route and has utilized a more appropriate selection of doses.

PNP also has been tested following inhalation exposure (Table 5). This study was not selected for inclusion as the key Repeated Dose Study, as it was conducted for a shorter (4-weeks) time period than the 90-day study referenced above. However, it too is considered "1- Reliable without restriction" and is included in the Robust Summary section of this Dossier.

It should be noted that no evidence of effects on the gonads was seen in either sex of rat in the studies cited above. Further, results of an 18-month chronic toxicity study in male and female mice (NTP, 1994) also cited in Table 5, resulted in no organ-related toxicity, including the gonads, up to the highest level tested (160 mg/kg/d, 3x/wk, 78 wks).

Conclusion - Thus, the Repeated Dose HPV Endpoint for PNP has been fulfilled with a 90-Day Subchronic study in rats deemed "1- Reliable without restriction". No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

3.1 Mutagenicity Testing (Ames test)

PNP has been extensively tested in the standard Ames assay for point mutations (ECB IUCLID, 2002; IPCS CICAD, 2000). PNP elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. The Haworth et al, (1983) study, conducted on behalf of the NCI/NTP program, has been summarized in the Robust Summary section of this Dossier and its results are referenced in Table 5. Its design and documentation are such that it is considered equivalent to OECD guideline # 471 and thus is "1- Reliable without restriction" for this assessment. Additionally, PNP has been tested in the secondary tier *Drosophila* Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program (NTP, 1994). Oberly et al, 1990 reported that PNP elicited no mutagenic activity when tested in a CHO-HGPRT forward mutation assay in mammalian cells.

Thus, it is concluded that adequate testing of sufficient quality has been performed on PNP to evaluate the Ames Test (Point Mutation) HPV Endpoint; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

As part of the NCI/NTP program (Galloway et al 1987), PNP was tested in the CHO cell *in vitro* assay to determine its capacity to induce chromosomal aberrations. A Robust Summary has been prepared for this study and its results are referenced in Table 5. PNP was negative for structural chromosome damage up to severely cytotoxic concentrations (>750 ug/ml) in a metabolic activation system-free environment. It did produce reproducible, dose-related and statistically significant increases in cells with structural chromosomal aberrations at levels of 1500 and 1700 ug/ml PNP after metabolic activation, although cells at these levels had undergone severe cell cycle delay. The quality of this study is considered to be "2- Reliable with restrictions", as it did not follow an established OECD protocol, yet was well documented and has been used for regulatory purposes. In a corresponding Sister Chromatid Exchange (SCE) assay

conducted in the same CHO cell test (Galloway et al. 1987), PNP produced no SCEs up to doses that caused severe cell cycle delay (25 ug/ml without S9 and 1700 ug/ml with S9).

The HPV Chromosomal Aberration Endpoint for testing of PNP has been fulfilled with adequately conducted and documented studies and no further testing is needed.

4.0 Reproductive Toxicity

A Two-Generation rat Reproduction Toxicity study of dermally applied PNP has been conducted (Table 5) and summarized in Dossier section VI - Robust Summaries. This study is considered adequate for assessment of this Endpoint as it has been accepted as such by IPCS (2000) and was judged "adequate" for US EPA pesticide reregistration (US EPA, 1998b). It was conducted under GLPs and followed OPPTS testing guidelines. Based on general acknowledgement of its scientific and regulatory acceptability, it has been judged as "1- Reliable without restriction" for purposes of this assessment. PNP was administered dermally in ethanol to groups of 12 male and 24 female rats at 50, 100 and 250 mg/kg/d. No indication of systemic toxicity was observed in either parental generation, although dermal irritation was observed at the site of application. No reproductive toxicity was observed at any dose tested in either the F1 or F2 matings. Both the adult systemic and reproductive toxicity NOELs are considered to be the highest dosage tested, i.e. 250 mg/kg/d.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled with conduct of a Two-generation rat study which followed regulatory testing guidance, was conducted under GLPs, and accepted in support of pesticide reregistration. Thus, no further testing for this HPV Endpoint is required.

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US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are appended

I U C L I D

Data Set

Existing Chemical	:	ID: 100-02-7
CAS No.	:	100-02-7
EINECS Name	:	4-nitrophenol
EINECS No.	:	202-811-7
TSCA Name	:	Phenol, 4-nitro-
Molecular Formula	:	C6H5NO3

Producer Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002

Substance Related Part

Company	:	Solutia Inc.
Creation date	:	04.04.2002
Memo	:	
Printing date	:	25.10.2002
Revision date	:	
Date of last Update	:	24.10.2002
Number of Pages	:	22
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

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1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= 114 ° C
Sublimation	:	
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol; also cited as a definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (2)

2.2 BOILING POINT

Value	:	> 279 ° C at
Decomposition	:	
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as Peer reviewed reference in HSDB (2002) for 4-nitrophenol; Cited as definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (19)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .0067 hPa at 20° C
Decomposition	:	
Method		other (calculated)
Year	:	1988
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as Peer reviewed reference in HSDB (2002) for 4-nitrophenol.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (11)

2.5 PARTITION COEFFICIENT

Log pow	:	<= 1.91 at ° C
Method		other (calculated)

Year	:	1985
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Value of <2.4 cited as definitive value in IPCS CIDAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (7)

2.6.1 WATER SOLUBILITY

Value	:	= 16000 mg/l at 25 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (18)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	other		
Light source	:			
Light spect.	:	nm		
Rel. intensity	:	based on Intensity of Sunlight		
Spectr. of subst.	:	lambda (max, >295nm)	:	290 nm
		epsilon (max)	:	
		epsilon (295)	:	
Conc. of subst.	:	10 mol/l at degree C		
Direct photolysis				
Halflife t1/2	:	= 5 - 7 day		
Degradation	:	% after		
Quantum yield	:			
Deg. Product	:			
Method	:	other (measured)		
Year	:	2002		
GLP	:	no data		
Test substance	:	no data		
Method	:	Dissolved in deionized water (1.18 g/100 ml) to which was added an acetate, phosphate or borate component to bring solution to pH 5, 7 or 9, respectively and introduced to sunlight (blind controls used). Analysis performed by GC using EC detector.		
Result	:	Half-life of 5.7 days at pH of 5, 6.7 days at pH of 7 and 13.7 days at pH 9.		
Reliability	:	(2) valid with restrictions Matches well vs. estimated value based on accepted model, ie AOP EPIWIN which estimated degradation to be 2.48 days, based on 12-hr day and 1.5e6 OH/cm3.		
Flag	:	Critical study for SIDS endpoint		

24.10.2002 (9)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other
Air (level I)	:	4.98
Water (level I)	:	36.3
Soil (level I)	:	58.7
Biota (level II / III)	:	
Soil (level II / III)	:	.0147
Method	:	other
Year	:	2002
Method	:	Level III Fugacity Model; EPIWIN:RQC from Syracuse Research Corp.; Physical chemical values utilized in this model were user entry measured values (mol wt=139.11; Henry's LC=1.3e-008 atm-m3/mole (user entered); Vapor Press=0.005 mm Hg (user entered); Log Kow=1.91 (user entered); Soil Koc=33.3 (calc. by model) obtained from reference sources. Emissions

rates were 1000 kg/hr for each of the three main compartments, air, water and soil.

```
Level III Fugacity Model (Full-Output):
=======================================
  Chem Name   : p-Nitrophenol
  Molecular Wt: 139.11
  Henry's LC  : 1.3e-008 atm-m3/mole (user-entered)
  Vapor Press : 0.005 mm Hg  (user-entered)
  Log Kow     : 1.91  (user-entered)
  Soil Koc    : 33.3  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       4.98            19           1000
   Water     36.3            20           1000
   Soil      58.7            20           1000
   Sediment  0.0147          60           0

             Fugacity    Reaction    Advection   Reaction
Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)
(percent)
   Air       7.37e-012    153         42          5.1
1.4
   Water     1.43e-014    1.06e+003   30.6        35.4
1.02
   Soil      2.33e-013    1.71e+003   0           57.1
0
   Sediment  1.61e-015    0.143       0.000248    0.00477
8.27e-006

   Persistence Time: 28.1 hr
   Reaction Time:    28.8 hr
   Advection Time:   1.16e+003 hr
   Percent Reacted:  97.6
   Percent Advected: 2.42

   Half-Lives (hr), (estimated from experimental data):
      Air:      19
      Water:    20
      Soil:     20
      Sediment: 60

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004
```

Reliability : (2) valid with restrictions
Estimated value based on accepted model. Second soil value was for sediment.

Flag : Critical study for SIDS endpoint

24.10.2002 (3)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum :

Contact time	:	
Degradation	:	1 - 100 % after 10 day
Result	:	other
Deg. Product	:	
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	no data
Method	:	Report contains a comparative assessment of a series of Biodegradabiltiy studies all performed in accord with OECD Guideline 301. Studies included: Coupled Units test, Zahn-Wellens test, MITI test, AFNOR test, Sturm test, OECD Screen test and Closed bottle test.
Result	:	With the exception of the Closed bottle test and the MITI test, which yielded low results, PNP was considered sufficient or even readily biodegradable in all other tests conducted. The degree (% DOC removed) for each test (days to complete) was: Coupled Units test - 100+/-4 % (7d); Zahn-Wellens test - 92%(10d); MITI test - 1%; French ANFOR test - 97%; Sturm test - 97%; and Closed bottle test - 60% (30d).
Test substance	:	No data cited in article, but typical technical grade PNP has purity of 99% and was likely used in these studies.
Reliability	:	(1) valid without restriction Use of OECD methodology acceptable for regulatory review and decision-making.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (5)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	c >= 5.8
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	other TS
Method	:	This study preceeded development of OECD Test Guideline 203 but was conducted in a manner consistent with that guideline. Groups of bluegill fingerlings (mean length of 2.8 cm); fish were not fed 48 h prior to nor during the 96 hr exposure period. Groups of 10 fish were added to glass vessels containing 15 l water at 5 test concentrations (8.7, 5.6, 3.7, 2.4 and 1.6 mg/L PNP dissolved in acetone. Both a negative control and an acetone-containing control group were also used. No aeration was performed during the test. Water temperature was maintained at 22+/-1%, with a pH ranging between 6.7-6.3. Dissolved oxygen ranged from 93% saturation at study start to 7% at study termination. Observations and mortality were checked every 24 hr. At the end of the study, test concentrations and observed mortality were converted to logarithms and probits, respectively, and analyzed by a least square regression method for determination of LC50 and CI at 24, 48, and 96 hr timepoints.
Result	:	All deaths occurred during the first 24 hr of the study, hence the LC50 and CI values for each of the study time points (24, 48, 96 hr) were the same, i.e. LC50 = 5.8 (3.7-9.2) mg/L. Mortality (%) observed at each PNP concentration was: 100% @ 8.7 mg/L, 10% @ 5.6 mg/L, and 0% @ 3.7 mg/L, 2.4 mg/L, 1.6 mg/L, untreated control and acetone control.
Test substance	:	Purity of 99%.
Reliability	:	(2) valid with restrictions This study was conducted prior to, but consistent with OECD Guideline # 203 and, US GLP guidelines effective in 1979 for nonclinical laboratory studies.Reduction in oxygen over time is not considered a factor in interpretation of results since all deaths (10%) occurred within first 24 hrs of study.
Flag	:	Critical study for SIDS endpoint

09.10.2002 (12)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m >= 13
EC50	:	c >= 22
Method	:	OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year	:	1980
GLP	:	no data
Test substance	:	other TS
Method	:	Methods used followed protocol as found in US EPA,1975 for Macroinvertebrate testing, which are consistent with OECD Guideline 202. D. magna, <24h old, were used as the tester strain. Culture water was

reconstituted as outlined in US EPA, 1975 guidance, such that it contained a total hardness of 173+/-13 mg/l as CaCO3 and a pH of 8.0+/-0.2. Temperature was maintained at 22+/-1 degree C. A stock solution of the chemical in distilled water was prepared and used to provide a series of graded concentrations (reportedly 5-8) for testing. PNP was added to 500 mL diluent water in 2-L jars to prepare for each test solution. The 500 mL volume of test solution was divided into three 150-mL aliquots to provide triplicate exposures at each concentration. Five Daphnids were randomly placed in each test solution within 30 min of preparation. A negative control was also tested. Meaurements were taken to confirm dissolved oxygen concentration, pH, and temperature in the high, medium and low test concentrations. Observations were made at 24 and 48 hours of exposure and any mortalities were recorded. Mortality data were used to calculate an LC50 and CI using a moving average angle method.

Result : LC50 (CI) values for 24 hr and 48 hrs were, respectively, 24 (22-26) mg/L and 22 (20-24) mg/L. ; The No Discernable Effect level was 13 mg/L. Dissolved oxygen concentrations ranged from 6.5-9.1 mg/L, pH values measured 7.4-9.4 units.

Test substance : Test compound purchased from commercial chemical supplier, hence technical grade PNP was likely used and had purity of 99%.

Reliability : (1) valid without restriction GLP compliance was not stated in the article but adequate documentation can be assumed as this study was performed for the US EPA under contract no. 68-01-4646.

Flag : Critical study for SIDS endpoint

23.08.2002 (10)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus subspicatus (Algae)
Endpoint : growth rate
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : no
EC10 : c >= 8
EC50 : c >= 32
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1985
GLP : no data
Test substance : other TS
Method : Following test guidelines set by OECD, 1983 and German Umweltbundesamt, 1982. Experiments were incubated at 22+/-2 degrees C. at constant photosynthetically effective light intensity. Due to a distinct change of pH value caused by inclusion of PNP in sterilized double distilled water used as the diluent in this study, the pH of the stock solution was adjusted to pH 7 using NaOH. Experiments were performed by preparing two parallel dilution series in 300-ml Erlenmeyer flasks containing a saturated test chemical solution, medium and 5 ml algae suspension of approx. 10E4 cells/ml. Each Erlenmeyer flask was shaken 2-3 times per day and continuously illuminated from the side by two fluorescent lamps. After 0, 72 and 96 hrs, the cell growth of a 10-mm layer of cell suspensions from each test culture and from the controls was measured at 578 nm using a spectrophotometer. The extinction units were converted to cell numbers using a standard curve and the cell numbers determined using the Utermoehl method. The concentration-effect relationships were plotted on semilogarithmic paper and EC10 and EC50 values determined graphically.

Test substance : Commercial grade PNP, and thus with purity of 99%.

Reliability : (1) valid without restriction
While not explicitly stated, the fact that this study was conducted according

to national (Ger) and international (OECD) test guidelines it most likely was conducted consistent with or actually followed GLP guidance.

Flag : Critical study for SIDS endpoint
23.08.2002 (6)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	50
Vehicle	:	other
Value	:	= 230 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Administered by gavage using propylene glycol as vehicle to 5 groups of rats (5 male and 5 female) given 70, 110, 171, 268 or 420 mg/kg/d; Clinical signs recorded 3X during first 8-hr after dosing and 2X daily for the remainder of the 14-d observation period. Body weights recorded on test days 0, 7 and 14. All survivors were necropsied on test day 15. Food and water administered ad libitum. LD50 and CI determined using method of Finney, DJ. 1971. Probit Analysis, Cambridge Univer. Press.
Result	:	LD50 +/- Confidence Limits (95%): 230 mg/kg (182-289 mg/kg); Deaths: 70 mg/kg (0/10), 110 mg/kg (0/10), 171 mg/kg (3/10), 268 mg/kg (8/10) and 420 mg/kg (8/10); Deaths all occurred within the first 8 hrs of dosing and exhibited the following clinical signs: convulsions, prostration and dyspnea prior to death; Clinical signs observed in survivors during the first three days after dosing included: tremors, ptosis, salivation and lethargy. No untoward effects were noted at necropsy of survivors.
Test substance	:	Technical grade purity of > 99%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

09.10.2002 (16)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	physiol. saline
Value	:	> 5000 mg/kg bw
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	One group of 5 male and 5 female rabbits were administered 5000 mg/kg/d test material on the shaved and abraded dermal surface. After administration the site was occluded and test material left in place for 24 hours. After test material removal, animals were observed for the remainder of the 14-d observation period. Clinical signs were recorded 3X during the first 8 hrs and 2X daily for the remainder of the study. Body weights were recorded on test days 0, 7 and 14. Necropsies were performed on all animals on test day 15. Food and water were administered ad libitum.

Result	:	No deaths occurred and no signs of systemic toxicity were seen during the study or at necropsy. Erythema and edema were observed during visual observations and at necropsy.
Test substance	:	Technical grade purity of > 99%
Reliability	:	(1) valid without restriction

09.10.2002 (17)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatment	:	Once daily throughout the exposure period
Post obs. period	:	None
Doses	:	0, 25, 70 and 140 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL	:	>= 25 mg/kg
LOAEL	:	= 70 mg/kg
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1989
GLP	:	yes
Test substance	:	other TS
Method	:	Groups of 20M and 20F S-D rats were administered 0, 25, 70 or 140 mg PNP/kg daily in distilled water for 13 weeks by gavage at a constant volume of 10 ml/kg. Dose levels were verified by spectrophotometric analysis. Mortality checks and signs of intoxication were made twice daily, and detailed clinical signs, individual body weights and food consumption recorded weekly. Pre and post study ophthalmoscopic examinations were also conducted on all animals available. At weeks 7 and 14 extensive hematology (RBC, RETIC, HGB, HCT, PLATELET, WBC, differential Leukocytes, and cell morphology) and serum chemistry (GLU, BUN, CREAT, AST, ALT, GGT, T PROT., ALBU, GLOB, CA, T BILI, PHOS, NA, POTAS, CL) parameters were conducted on blood samples from 10 animals/sex/group. No urinalysis was performed. At termination brain, liver, kidney, spleen and testes with epididymides were weighed for all survivors and a full necropsy performed. A full set of approx. 40 tissues and organs (including gonads) were collected from all surviving animals and sections were examined microscopically from these tissues for the control and high dose animals. Microscopic examination of tissues was also performed on tissues of premature deaths exhibiting gross autopsy findings. Temperature, lighting and humidity were controlled throughout the study. Body weights and weight gains, food consumption, hematology and clinical chemistry parameters and organ weights (absolute and relative) were

initially analyzed using Levine's test of homogeneity of variances. If nonhomogeneous, data were transformed and then analyzed via ANOVA ($p<0.05$). Dunnett's t-test (2-tail, $p<0.05$) was used to compare treated and control groups. Cumulative survival was assessed using the National Cancer Institute statistical package and analyzed for trend.

Result : Early deaths were seen in groups of male and female rats given 70 and 140 mg/kg/d PNP. Total premature deaths observed in 0, 25, 70 and 140 mg/kg males were 0,0,1, 15, respectively; for females - 0,1,1,6, respectively; Several of these premature deaths (1-70 mg/kg male, 2 @ 140 mg/kg male, 3 @ 140 mg/kg female) died shortly after bleeding at wk 7, which likely exacerbated deaths, while 1 HD male was found to have died from gavage error. All other deaths at 70 mg/kg and 140 mg/kg were considered related to PNP exposure as they exhibited significant clinical signs of toxicity (pale appearance, languid behavior, prostration, wheezing and dyspnea), died shortly after dosing and exhibited moderate to severe congestive liver, kidney, lungs and adrenal cortex pathology (which correlated with necropsy findings) after microscopic examination; The presence of clinical signs of toxicity and absence of specific histopathological changes in these premature deaths suggests a relationship to acute pharmacologic/toxicologic effect. The single premature death observed in the LD female group was not considered treatment-related as there were no clinical signs observed, it did not die shortly after dosing (was found dead overnight) and had little in the way of organ congestion. Significant increases were observed in segmented neutrophils and absolute monocytes and eosinophil counts, as well as polychromasia of erythrocytes in 140 mg/kg animals of both sexes; these findings were considered of no toxicological significance. No treatment-related effects were observed in clinical signs, body weights, food consumption, ophthalmoscopic examination, organ weights or histopathology of survivors. Specifically, no effects were observed on gonads in this study. A NOEL was established as 25 mg/kg/d.

Test substance : Purity of 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
09.10.2002 (15)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 4 weeks
Frequency of treatment : 6 hr/d, 5 days/week
Post obs. period : none
Doses : 0, 1, 5, and 30 mg/m3
Control group : yes
NOAEL : >= 5 mg/m³
LOAEL : = 30 mg/m³
Method : OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year : 1984
GLP : yes
Test substance : other TS
Method : Groups of 15 male and 15 females S-D rats were exposed to target concentrations of 0, 1, 5 or 30 mg/m3 of PNP dust via whole body exposure in 1000 L glass and stainless steel chambers. Chamber concentrations were generated via use of a Wright dust feed and determined 3X daily by gravimetric analysis. Particle size determinations were measured weekly. Food and water were available ad libitum at all times other than during exposure. Temperature and humidity, as well as light:dark cycle were controlled. Animals were observed twice daily for mortality and signs of toxicity. Each animal was carfully examined and

weighed weekly. Hemoglobin and methemoglobin concentrations were determined by orbital sinus during week 2. Ophthalmic exams were conducted just prior to terminal sacrifice on all animals. The following hematology (RBC, HCT, HGB,PLATELETS, RBC morph, and total and differential leukocyte counts, and clotting time) and blood chemistry (ALT, AST, BUN, TOT BILI, GLU, LD, CHOL, NA, POTAS, CA, CL, PROT, ALBU, GLOB) were evaluated after 4 weeks. No urinalysis was performed. Complete necropsies were conducted on all animals on test. The following organ weights were recorded: lungs, liver, kidneys, brain, heart, adrenals, spleen and testes with epididymides. Thymus wt was not recorded. Histopathological examinations were conducted on approximately 40 tissues and organs, and all gross lesions observed at necropsy, on all high dose and control animals. Clinical pathology, hematology, weekly body weights and weight gains, organ weights and weight ratios of control groups were compared statistically to treated groups of the same sex. Box test was used to determine homogeneity of variances followed by a 1-way classification by ANOVA if variances were homogeneous or use of rank transformation if nonhomogeneous. If found significant ($p<0.05$) Dunnett's t-test was used to compare groups ($p<0.05$).

Result : Mean gravimetric chamber concentrations were 1.09, 5.27, and 29.2 mg/m3. MMD ranged from 5.4 -6.9 u. Prestudy analysis indicated that the PNP dust was homogeneously distributed in the stainless steel chamber. No deaths occurred during the study. Except for dose-related yellow staining attributed to test material, no abnormal physical observations were noted. Ophthalmoscopic e xaminations revealed 11 cases of diffuse anterior capsular cataracts only in HD males and females. Corneal keratitis sicca (inflammation and drying of the cornea and conjuctiva) was noted in 3 HD animals. Periodic changes in body weights were seen inconsistently and in opposite directions for each sex and thus not considered tretment-related. No consistent, dose-related effect was noted in METH values, while some very slight changes in HGB and HCT were seen in HD males. The relationship of these effects to PNP treatment is unclear. No treatment-related effects were seen in other hematologic or clinical chemistry parameters. No gross or microscopic pathological effects or organ weight changes were noted that were attributed to PNP. No effects on the gonads was observed. A NOEL was established as 5 mg/m3.

Test substance : Purity of 99 %.

Reliability : (1) valid without restriction

09.10.2002 (13)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 4 weeks
Frequency of treatment : once daily for the entire test period
Post obs. period : none
Doses : 0, 1, 10, 50, and 100 mg/kg
Control group : yes, concurrent vehicle
NOAEL : >= 50 mg/kg
LOAEL : >= 100 mg/kg
Method : other
Year : 1989
GLP : yes
Test substance : other TS
Method : Groups of 5 male and 5 female S-D rats were administered PNP in distilled water by gavage at doses of 0, 1, 10, 50 and 100 mg/kg at a constant volume of 10 ml/kg. Daily clinical signs were recorded and individual body weights and food consumption were taken weekly for all animals. Hematological (HGB, HCT, RBC, TOT /DIFF LEUKO, MET HGB) and clinical pathological (BUN, GLU, CREAT, ALT, ATS, T PROT, ALBU,

GLOB, T BILI, PHOS, NA, K, CL) parameters were measured prior to study termination after 4 weeks. Gross necropsy examinations were conducted at the terminal sacrifice and brain, liver, kidneys, spleen and testes with epididymides were trimmed and weighed. Collected tissues (approx. 40/animal) were preserved and gross lesions, kidneys, livers and spleen were prepared from all animals and examined microscopically. Dosing solutions were analyzed by spectrophotometric means for stablity and concentration.

Result : Analysis of dosing solutions indicated stability and accuracy. One female rat at the 100 mg/kg dose level died shortly after bleeding followed by dosing and is likely treatment-related. Mean body weights and food consumption in treated groups were comparable to control values. No changes were observed in hematology or clinical chemistry values between treated and control groups. No clinical signs of toxicity were observed in survivors. Organ weights, necropsy findings and microscopic examination of treated rats were similar to controls.

Test substance : Purity of 99 %.

Conclusion : This study was a range-find study to set dose levels for study no. HL-88-372. As such, no statistical treatment of data was ascertained.

Reliability : (2) valid with restrictions

09.10.2002 (14)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test

System of testing : Salmonella typhimurium strains TA100, TA98, TA1535 and TA1537

Concentration : 0, 10, 33, 100, 166, 333, 666, 1000 ug/plate

Cycotoxic conc. : 1000 ug/plate (TA100)

Metabolic activation : with and without

Result : negative

Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"

Year : 1983

GLP : yes

Test substance : other TS

Method : Methodology used by NTP based on Ames test plate incorporation assay and consistent with OECD 471. All tests were run in duplicate and three plates were assayed at each dosage for each run both with and without metabolic activation; S9 obtained from male S-D rats injected with Arochlor 1254 (500 mg/ml) five days before they were killed; all tester strains obtained originally from B. Ames; the high dose was designed to produce toxicity (reduced background lawn or solubility limits; sterile DSMO was used as the solvent; negative (solvent) and positive controls (2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium azide and 9-aminoacridine) used were appropriate to detect mutagenicity with or without metabolic activation in each of the 4 tester strains used. A positive response was detected if a reproducible, dose related increase (>2X) was seen in revertant colonies according to a model described by Margolin et al 1981.

Result : No increase in revertants were observed with or without metabolic activation in any of the 4 tester strains.

Test substance : Purity = 99%.

Reliability : (1) valid without restriction
While no statistical methods were used, none were needed to visually inspect and render a conclusion of no increases observed in revertants in any tester strain; further, these findings are consistent with other literature citations using similar methodology

Flag : Critical study for SIDS endpoint

09.10.2002 (8)

Type	:	Chromosomal aberration test
System of testing	:	Chinese Hamster Ovary cell culture
Concentration	:	100 to 2500 ug/ml
Cycotoxic conc.	:	not stated
Metabolic activation	:	with and without
Result	:	positive
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	Study performed under auspices of US NTP program. Doses were based on a preliminary test of cell survival 24 hr after treatment. Cells were collected 10.5 h after treatment by mitotic shaking-off. Slides stained with Giemsa and coded. 100 cells were scored from each of the 3 highest dose groups having sufficient metaphases for analysis (cells with 19-23 metaphases chosen); Positive control groups treated with triethylenemelamine, mitomycin C or Cyclophosphamide), solvent control also used.. Aberrations were typed and recorded separately but analyzed grouped into categories of simple (breaks and terminal deletions), complex (rearrangements and exchanges) and other (i.e pulverized chromosomes). Gaps and endoreduplications were recorded but not included in totals. Aberrations in polyploid cells were not scored. Linear regression of the percentage of cells with aberrations vs. the log-dose was used as the test for trend. A binomial sampling assumption was used and data were analyzed according to the method of Margolin et al Environ Mutag 8:183 (1981). P values were adjusted by Dunnett's method to take multiple dose comparisons into account.
Remark	:	In a concurrent study PNP was negative for SCE induction up to doses that caused severe cell cycle delay (25 ug/ml -S9; 1700 ug/ml +S9).
Result	:	No treatment-related increase in the frequency of structural aberration were noted up to severe cytotoxic levels (>750 ug/ml -S9; Reproducible , dose-related and significant increases in cells with structural chromosomal aberrations were seen at test levels of 1500 to 2000 ug/ml +S9 that induced severe cell cycle delay.
Test substance	:	Purity of 99 %.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

15.10.2002 (4)

5.6 GENETIC TOXICITY 'IN VITRO'

5.7 CARCINOGENITY

5.8 TOXICITY TO REP RODUCTION

Type	:	Two generation study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	F0: males - 113 doses; females - 118 doses; F1: males - 190 doses; females - 180 doses
Frequency of treatment	:	once per day, 5 days per week
Premating exposure period		
Male	:	140 days (100 doses)

Female	:	140 days (100 doses)
Duration of test	:	Through prebreeding, breeding ,gestation, lactation and development through two full generations (1 litter per generation), F2 pups observed through 30 days postweaning.
Doses	:	50, 100, and 250 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	> 250 mg/kg bw
NOAEL F1 Offspr.	:	> 250 mg/kg bw
NOAEL F2 Offspr.	:	> 250 - mg/kg bw
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	other TS
Method	:	5-Week old Charles River CD rats began treatment, consisting of 120 female and 60 male rats housed in wire mesh caging. Humidity, temperature and light:dark cycle were controled throughout the study. Water and food were available ad libitum. After random assignment, each of the five test groups began the study (Fo generation) with 24 females and 12 male rats per group. All rats were clipped free of hair along the dorsal body line and reshaved as necessary to allow good dermal contact with the test agent. Dosing periods were lengthened over the periods recommended by EPA guidelines to compensate for a 5-day per week dosing period in this study. Test agents were applied dermally using appropriate-sized syringes, once daily, 5 days /week. Animals were individually weighed at the beginning of each study and dose levels adjusted. F0 animals were treated for the first 140 days of the study (100 applications each). Thereafter, one half of the females in each group were paired with corresponding males until either positive mating was achieved (presence of sperm plug and confirmed by vaginal smear) or it became evident that the pair would not mate. In the latter cases additional cohousing occurred until it became apparent that no further mating would ensue. After successful mating, males and females were separated; F0 males were held until all mating ceased, at which time they were sacrificed and testes, epididymis and skin sections were taken for histopathologic evaluation. Dosing of F0 females continued through the breeding, gestation and lactation periods. Females dosed during gestation were based on the last premating weight. Approximately 21 days after birth, the F1 generation was weaned and F0 females sacrified with their ovaries, uterus and skin sections taken for histopathologic examination. 13 males and 26 females from the F1 generation were randomly selected for continued dosing and breeding in a manner similar to the F0 generation. Application of test materials continued over the next 168 days (120 applications each). Following this period, the F1 rats were mated in a procedure corresponding to the mating of the F0 parental animals. Five males and 5 female pups from the F1 generation were selected at weaning for complete necropsy exam. An additional 5 F2 males and 5 F2 females from each group were randomly selected and retained in wire cages for 30 days after weaning. Dosing of all F1 rats continued throughout breeding, gestation, lacatation and until 30 days after all F2 rats had been weaned. Thereafter, all F1 rats and remaining F2 rats were submitted for complete necropsy. All animals dying spontaneously during the course of the study were submitted for necropsy. All rats which underwent necropsy were subjected to histopathological assessment of the following tissues and organs: (brain, spinal cord, eye, salivary gland, heart, thymus, thyroid, lungs, bronchi, esophagus, stomach, small intestine, large intestine, pancreas, adrenal glands, kidneys, liver, testes, epididymis, urinary bladder, male accessary glands, ovaries, corpus uteri, cervix uteri, spleen, lymph nodes, sernum, femur, skeletal muscle, mammary gland, treated skin and untreated skin. Organ weights were recorded for scheduled sacrifies from F1 and F2 animals: liver, kidneys, heart, gonads (F0 males also), and brain. Observations for toxic signs, breeding and nesting behavior were recorded daily for all animals. Weights of all dosed rats were recorded weekly.

Breeding and litter observations included: litter size, individual pup weights and viability at birth and on days 4, 7, 14, and at weaning. The following indices were calculated to assess reproductive success: fertility (no. of pregnancies/no. mated) gestation (% of pregnancies resulting in birth of live litters), viability (pups surviving at least to day 4 of life) and lactation (pups surviving at least to day 21 of life). Group-wise statistical ($p < 0.05$) comparisons were made of body weights, absolute and relative organ weights.
The High dose (250 mg/kg/d) was selected based on a range-find study indicating this level to be 1/4 LD50 dermally, and would allow sufficient survival; both an ethanol vehicle (used at 500 mg/ml) control group (0.5 ml/kg/d) and a saline control group (0.5 ml/kg/d) were also evaluated concomittantly. Multigeneration study methodology was modified (dosing took place 5 d/wk rather than 7 d/wk) from test guidelines recommended in TFX Collins Handbook on Teratology, Vol. IV, Chapter 7: Multigeneration Reproduction Studies. 1978.

Result : All F0 and F1 rats dosed dermally with PNP or ethanol exhibited a pattern of dermal irritation consisting of varying degrees of erythema, scaling, scabbing and cracking ; some degree of dose-response was noted in PNP-treated groups. No treatment-related m ortality was observed in either the F0 or F1 parental generation, and no effects of treatment were noted in body weights in these groups. No evidence of effects in mating, pregnancy, behavior,and growth were found in parents or subsequent F1 and F2 generations.All group-wise comparison of organ weights, including gonads, were unremarkable. No evidence of histopathologic alterations was seen in any tissue examined, including the gonads.

Test substance : Purity of test substance used - 99.1%

Reliability : (1) valid without restriction
Study sufficiently adequate to be accepted to fulfill US EPA pesticide reregistration requirement for reproductive toxicity endpoint.

23.08.2002 (1)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(1) Angerhofer, R. 1985. USEHA. Army Environmental Hygiene Agency. Effects of dermal application of Paranitrophenol on the reproductive function of rats. Study no. 75-51-0047-85. 1583 p. Also summarized in US EPA R.E.D. FACTS Document, EPA-738-F-97-016, Jan. 1998.

(2) Budavari, S. (ed) 1996. The Merck Index - an encyclopedia of chemicals, drugs and biologicals. Whitehouse Station, NJ. p.1138.

(3) EPIWIN. 2002. Syracuse Research Corp., Syracuse, NY. Version 3.10 modeled after Meylan, W. 1993; adopted from methodology described by MacKay et al, 1996, Environ. Toxicol. Chem 15(9):1618-1637.

(4) Galloway, SM, Armstrong, MJ, Reuben, C, Colman, S, Brown, B, Cannon, C, Bloom, AD, Nakamura, F, Ahmed, M, Duk, S, Rimpo, J, Margolin, BH, Resnick, MA, Anderson, B and Zeiger, E. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese Hamster Ovary Cells: Evaluation of 108 Chemicals. Environ Mol Mutagen 10:1-175. Also in: NTP Technical Report Series No. 417.

(5) Gerike, P and Fischer, WK. 1979. A correlation study of biodegradability determinations with various chemicals in various tests. Ecotoxicol Environ Safety 3:159-173.

(6) Geyer, H, Scheunert, I and Korte, F. 1985. The effects of organic environmental chemicals on the growth of the algae Scenedesmus subspicatus. Chemosphere 14:1355-69.

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(8) Haworth, S, Lawlor, T, Mortelmans, K, Speeck, W, and Zeiger, E. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1:3-142. Also in NTP Technical Report Series No. 417

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(10) LeBlanc, G. 1980. Acute toxicity of priority pollutants to water flea (Daphnia magna). Bull Environ Contam Toxicol. 24:684-691.

(11) Schwarzenbach, RP, Stierli, R, Folsom, BR, Zeyer, J. 1988. Compound properties relevant for assessing the environmental partitioning of nitrophenols. Environ Sci Technol. 22:83-92.

(12) Solutia Study No. BN-77-126. Acute (96 hr) Toxicity of p-Nitrophenol to Bluegill.

(13) Solutia study no. HL-82-242. Subacute Dust Inhalation Toxicity Study in Rats: p-Nitrophenol.

(14) Solutia study no. HL-88-347. 4-Week Dose Range-Finding Study in Rats with p-Nitrophenol. [EPA no. 86-890000362]

(15) Solutia study no. HL-88-372. Subchronic Toxicity Study in Rats with Para-Nitrophenol.[EPA document no. 40-8915314]

(16) Solutia study no. ML-82-131a. Acute Oral Toxicity of p-Nitrophenol to Rats.

(17) Solutia study no. ML-82-131b. Acute Dermal Toxicity of p-Nitrophenol to Rabbits.

(18) Verschueren, K. 1996. Handbook of environmental data on organic chemicals. 3rd Ed. New York, NY. Van Nostrand Reinhold Co. p. 1399.

(19) Weast, RC (ed). 1988. Handbook of chemistry and physics, 68th ed. Boca Raton, Fla. CRC Press, Inc. p. C-414

7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT

201-14667

NCIC HPV
Sent by: Mary-Beth Weaver

08/14/2003 02:29 PM

To: NCIC HPV, moran.matthew@epa.gov
cc:
cc:
Subject: Environmental Defense comments on 4-Nitrophenol (CAS# 100-02-7)

Richard_Denison@environmentaldefense.org on 08/14/2003 09:44:42 AM

To: oppt.ncic@epamail.epa.gov, hpv.chemrtk@epamail.epa.gov, Rtk Chem/DC/USEPA/US@EPA, Karen Boswell/DC/USEPA/US@EPA, frjoha@solutia.com
cc: lucierg@msn.com, kflorini@environmentaldefense.org, rdenison@environmentaldefense.org

Subject: Environmental Defense comments on 4-Nitrophenol (CAS# 100-02-7)

(Submitted via Internet 8/14/03 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, lucierg@msn.com and frjoha@solutia.com)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for 4-Nitrophenol (CAS# 100-02-7).

The test plan and robust summaries for 4-nitrophenol (NP), also termed p-nitrophenol, was submitted by Solutia, Inc. NP is apparently manufactured by the sponsor at a single site and sold to customers at other sites for the purpose of full chemical conversion into other industrial chemicals. However, use practices of the customers are not monitored, so it may have other applications not reported in this test plan.

NP possesses high acute toxicity and can cause methemoglobinemia in workers. The sponsor states that practices are in place to minimize worker exposure, but they are not detailed nor is their any information presented on maximum allowable concentrations in the workplace. Likewise, no data are provided on environmental releases. If NP is synthesized in a closed system, as the sponsor maintains but does not document in the test plan, any releases during production should be minimal. Transport (including export) and conversion as a chemical intermediate are mentioned but potential releases from such activities are not characterized in the test plan.

The test plan is well-written and organized and the sponsor claims that no new studies are needed to fulfill HPV requirements. We agree with this claim with one exception. Based on the information presented in the robust summaries, a developmental toxicity study needs to be conducted. Specific comments are provided below:

1. Existing studies on environmental fate and distribution and ecotoxicity studies are adequate for screening level purposes. The sponsor states that although NP is resistant to hydrolysis, it should not bioaccumulate in aquatic organisms. We agree with the sponsor for the reasons stated in the test plan. We also note that NP is rapidly conjugated by most organisms and this process renders the molecule non-toxic and water-soluble.

2. Acute toxicity studies using multiple routes of exposure indicate that NP is toxic when administered orally or via inhalation. In contrast, it is not acutely toxic when administered dermally.

3. Existing repeat dose studies are more than adequate to fulfill HPV requirements, as there are multiple studies in multiple species. These studies also indicate that NP is toxic via the inhalation and oral routes

but not the dermal route.

4. There are substantial studies which have examined the in vitro genetic toxicity of NP, but no in vivo studies -- although there are in vitro studies on chromosomal aberrations in CHO cells. Taken together, we agree with the sponsor that in vivo genetic toxicity studies on NP are not necessary.

5. The robust summary contains only a 2-generation reproductive study on NP administered via the dermal route. No developmental toxicity studies were reported. Since dermally-administered NP is not acutely toxic and no information was provided on the systemic levels of NP following dermal administration, the reproductive/ developmental dataset is inadequate for screening level purposes. We do note that no histological alterations of reproductive organs were detected in the oral or inhalation repeat dose studies, so a new reproductive toxicity study is not needed. However, an oral or inhalation developmental toxicity study is warranted, as data on this endpoint are not available.

Thank you for this opportunity to comment.

George Lucier, Ph.D.
Consulting Toxicologist, Environmental Defense

Richard Denison, Ph.D.
Senior Scientist, Environmental Defense

PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE
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August 14, 2003

Marianne L. Horinko, Acting Adminstrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for 4-Nitrophenol, or PNP

Dear Administrator Horinko:

The following comments on Solutia's test plan for the chemical 4-Nitrophenol, also known as para-Nitrophenol or PNP, are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

Solutia, Inc. submitted its test plan on April 17, 2003 for the chemical PNP (CAS No. 100-02-7), which is manufactured in the U.S. by Solutia at a single site. PNP is then sold to a limited number of customers for the express purpose of full chemical conversion into other industrial chemicals used as dyes/pigments, pharmaceuticals, analgesics, and adhesives. Solutia has submitted a comprehensive analysis of PNP by compiling substantial amounts of existing data from a variety of sources. In addition, this company considers potential exposure to PNP and appropriately concludes that very limited occupational or environmental exposure is expected to occur. When considering the toxicity of a chemical, these approaches demonstrate a thoughtful analysis by Solutia. Information from existing data for physicochemical properties, environmental fate, and human and environmental effects of PNP have led Solutia to conclude that no additional testing is necessary under the HPV Challenge program.

We commend Solutia's efforts in drawing on all available information from a myriad of sources to meet the SIDS endpoints for the chemical PNP. This approach is consistent with the EPA's stated goals of maximizing the use of existing data in order to limit additional animal testing. At this time we would like to point out that although no developmental toxicity data for PNP was included in the test plan, results from the two-generation rat reproductive toxicity study show no evidence of developmental toxicity. Data from individual pup weights and viability at birth, day 4, day 7, day 14 and at weaning provide strong evidence that PNP does not pose a developmental hazard.

However, if EPA wishes Solutia to further investigate potential developmental toxicity, this would be the perfect opportunity for the EPA and Solutia to agree to conduct the rodent embryonic stem cell test (EST), an *in vitro* embryotoxicity test method validated by ECVAM in 2002. Data from the EST together with the reproductive toxicity data could be used to address this SIDS endpoint. The Institute for In Vitro Sciences, Inc. in Gaithersburg, MD is currently offering the EST test to clients in the U.S. and elsewhere. We sincerely hope that Solutia will take a leadership role in pursing the EST test to meet the developmental toxicity endpoint in the HPV program, thereby sparing large numbers of animals. Thank you for your attention to these comments. I may be reached at 202-686-2210, ext. 327, or via e-mail at meven@pcrm.org.

Sincerely,

Megha Even, M.S.
Research Analyst

Chad B. Sandusky, Ph.D.
Director of Research

August 20, 2003

Frederick R. Johannsen
Technical Contact
Solutia, Inc.
575 Maryville Centre Drive
St. Louis, MI 63141

Dear Mr. Johannsen:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 4-Nitrophenol posted on the ChemRTK HPV Challenge Program Web site on April 17, 2003. I commend Solutia, Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Solutia, Inc. advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
4-Nitrophenol

Summary of EPA Comments

The sponsor, Solutia, Inc., submitted a test plan and robust summaries to EPA for 4-Nitrophenol (PNP; CAS No. 100-02-7) dated April 9, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on April 17, 2003.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for melting point, octanol/water partition coefficient and water solubility are adequate for the purposes of the HPV Challenge Program. The submitter needs to re-examine the boiling point and vapor pressure data.

2. Environmental Fate. The submitter needs to address some deficiencies and errors for photodegradation, biodegradation, and fugacity. The submitter needs to incorporate hydrolysis information in robust summary format.

3. Health Effects. Adequate data are available for acute, repeated-dose, genetic, and reproductive toxicity endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide additional information for developmental toxicity.

4. Ecological Effects. Available data are adequate for the purposes of the HPV Challenge Program.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 4-Nitrophenol Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, octanol/water partition coefficient and water solubility are adequate for the purposes of the HPV Challenge Program.

Boiling point. The boiling point for 4-nitrophenol is given as >279 °C in Table 2 on page 9; however, according to handbook sources this value reflects decomposition (Verschuren, K. 2001. Handbook of environmental data on organic chemicals, 4th ed. New York, NY: John Wiley & Sons, p. 1636). The submitter needs to state that this is a decomposition temperature.

Vapor pressure. The submitter obtained a calculated vapor pressure of 0.0067 hPa (0.0050 mmHg) at 20 °C from HSDB 2002. However, the value for PNP from Schwarzenbach et al. (1988) was misreported in the HSDB. The value 0.0050 mmHg corresponds to the vapor pressure at 20 °C for the subcooled liquid of 2,4-dinitrophenol.

Schwarzenbach et al. also reported extrapolated vapor pressures for 4-nitrophenol at 20 °C of 1.10×10^{-6} atm (8.33×10^{-4} mmHg) for the subcooled liquid, and 1.29×10^{-7} atm (9.79×10^{-5} mmHg) for the solid. The value for solid 4-nitrophenol can satisfy the endpoint in this case.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

Photodegradation. The submitter provided values of 5.7 days (pH 5), 6.7 days (pH 7), and 13.7 days (pH 9) (Hustert et al. 1981). The submitter indicates that these values compare favorably with an AOPWIN estimated value of 2.48 days based on a 12-hr day and 1.5 x 10^6 OH/cm^3. This comparison is in error. The data in Hustert et al. (1981) are for direct photolysis in aqueous solution by sunlight. The estimations from AOPWIN provide half-lives for the reactions of vapor phase 4-nitrophenol with photochemically generated hydroxyl radicals. The submitter needs to address this error.

Stability in water. While EPA agrees that this chemical is stable to hydrolysis, the submitter needs to include this information in a robust summary. Furthermore, the submitter needs to indicate that 4-nitrophenol does degrade in water upon exposure to sunlight, referencing the relevant data presented in the photodegradation section.

Biodegradation. The submitter needs to provide a detailed description of each test including the OECD Screening test, and resolve other issues identified under the comments on the robust summaries.

Fugacity. The submitter used an incorrect vapor pressure in the input parameters. The correct value for 4-nitrophenol is 9.79x10^{-5} mmHg (see vapor pressure section, above). The submitter's Henry's law constant is not consistent with the experimental value cited in the PHYSPROP database, 4.15x^{-10} atm-m^3/mole (Parsons et al. 1971). The submitter used half-lives in air, water, soil, and sediment that were very short, and did not explain why these were used. The submitter needs to address these vapor pressure, Henry's law constant, and half-life input issues.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for acute, repeated-dose, genetic, and reproductive toxicity endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide additional information for the developmental toxicity endpoint.

Repeated-dose toxicity. The submitter needs to include in the robust summaries the 18-month chronic toxicity study in mice (NTP, 1994) discussed in the test plan.

Genetic toxicity (gene mutation). The submitter needs to provide separate robust summaries for the *Drosophila* sex-linked recessive lethal assay (NTP, 1994) and the NTP's CHO-HGPRT forward mutation assay (Oberly et al, 1990), which are discussed as supporting data in the test plan.

Genetic toxicity (chromosomal aberration). The submitter needs to provide the SCE assay as a separate robust summary.

Developmental toxicity. The submitter needs to discuss the developmental toxicity criteria for the submitted 2-generation reproductive toxicity study. Since the study was conducted with much lower doses than those recommended by the OECD guidelines for the dermal route, and did not elicit any maternal toxicity at the highest dose tested, the submitter needs to provide information on the selection of doses and exposure route.

The test plan and Tables 1 and 5 in the test plan need to specifically address the developmental toxicity endpoint.

Ecological Effects (fish, invertebrates, and algae)

The studies submitted on fish, invertebrates and algae adequately address these endpoints.

Specific Comments on the Robust Summaries

Generic Comments

Some of the definitive values (*e.g.,* EC50/LC50 and NOAELs/LOAELs) were reported as greater than or equal to (≥) in the respective fields. The submitter needs to remove the greater than (>) sign.

Environmental Fate

Biodegradation. (a) The submitter indicates that it used five OECD guideline 301 methods. However, the only tests that seem to follow OECD Guideline 301 are the Sturm test (301 B), the OECD Screen test (301 E), and the Closed Bottle test (301 D). This point needs clarification. (b) The Zahn-Wellens test is OECD Guideline 302 B for determining inherent biodegradability, not ready biodegradation as indicated in the robust summary. (c) The submitter needs to indicate clearly and accurately which tests provide inherent biodegradation results and which provide ready biodegradation results, rather than categorize them all as ready biodegradation. (d) The degradation time periods for the MITI test, the AFNOR test, and the Sturm test are missing.

Ecological Effects

Algae. The submitter needs to provide the test concentrations used in the algal study.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

Anh Nguyen
03/25/04 09:39 AM

To: NCIC HPV@EPA
cc:
Subject: Response to Comments on HPV Submission for p-nitrophenol, CAS No. 100-02-7

----- Forwarded by Anh Nguyen/DC/USEPA/US on 03/25/2004 09:33 AM -----

"Lederer, Don A" <dalede@solutia.com>
03/25/2004 09:25 AM

To: NCIC OPPT@EPA, Rtk Chem@EPA
cc: "Downes, James E" <jedown@solutia.com>, rauckman@toxicsolutions.com
Subject: Response to Comments on HPV Submission for p-nitrophenol, CAS No. 100-02-7

Attached are documents pertaining to our response to EPA comments on the HPV Submission for p-nitrophenol, CAS No. 100-02-7.

Regards,

Don Lederer, CHMM
Product Stewardship Manager
Solutia Inc.



314/674-1113 PNP HPV RS Rev3-5-04.rtf PNP Response To Comments.doc PNP HPV TP Rev3-5-04.doc

Cover Letter Response to Comments.

201-15148

Don Lederer, CHMM
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March 25, 2004

Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

RE: **HPV Chemical Challenge Program**
Response to Comments
AR-201-14390
p-nitrophenol
CAS No. 100-02-7

We are pleased to provide the Agency our responses to comments received from EPA and other stakeholders on our referenced HPV Chemical Challenge submission for p-nitrophenol, CAS No. 100-02-7, which you will find attached. We are forwarding responses to the specific comments, along with a revised Test Plan and Robust Summary package.

Thank you for your consideration. Please contact me directly should there be any question related to this submission.

Sincerely,

Regards,

Donald A. Lederer, CHMM
Product Stewardship Manager

Response to Comments on HPV Challenge Submission

4-Nitrophenol
CAS Number 100-02-7

Solutia Inc.
March 25, 2004

EPA Comments

Specific Comments on the Test Plan

COMMENT 1: *Boiling point*. The boiling point for 4-nitrophenol is given as >279 C in Table 2 on page 9; however, according to handbook sources this value reflects decomposition (Verschuren, K. 2001. Handbook of environmental data on organic chemicals, 4th ed. New York, NY: John Wiley & Sons, p. 1636). The submitter needs to state that this is a decomposition temperature.

RESPONSE: Decomposition was indicated and the reference was brought up to date since the current Handbook of Chemistry and Physics does not list a boiling or decomposition point for PNP.

COMMENT 2: *Vapor pressure*. The submitter obtained a calculated vapor pressure of 0.0067 hPa (0.0050 mmHg) at 20 C from HSDB 2002. However, the value for PNP from Schwarzenbach et al. (1988) was misreported in the HSDB. The value 0.0050 mmHg corresponds to the vapor pressure at 20 C for the subcooled liquid of 2,4-dinitrophenol.

Schwarzenbach *et al*. also reported extrapolated vapor pressures for 4-nitrophenol at 20 C of 1.10x10-6 atm (8.33x10-4 mmHg) for the subcooled liquid, and 1.29x10-7 atm (9.79x10-5 mmHg) for the solid. The value for solid 4-nitrophenol can satisfy the endpoint in this case.

RESPONSE: Thank you for the excellent analysis. The vapor pressure has been reported over a range of values from different sources but the extrapolated Schwarzenbach value that you cite for solid material is probably the most accurate and appropriate. We have used the recommended value.

We would like to point out that the U.S. EPA has "Air Toxics" information on their website giving the following: "The vapor pressure for 4-nitrophenol is 0.0003 mm Hg at 30 °C, and it has a log octanol/water partition coefficient (log K_{ow}) of 1.91." http://www.epa.gov/ttn/atw/hlthef/nitrophe.html

The correspondence of the EPA 30°C value (0.0003 mm) to the Schwarzenbach 20° value (0.0000974 mm) is actually quite close if the Antoine equation is used for extrapolation between the two temperatures.

COMMENT 3: *Photodegradation*. The submitter provided values of 5.7 days (pH 5), 6.7 days (pH 7), and 13.7 days (pH 9) (Hustert et al. 1981). The submitter indicates that these values compare favorably with an AOPWIN estimated value of 2.48 days based on a 12-hr day and 1.5 x 106 OH/cm3. This comparison is in error. The data in Hustert et al. (1981) are for direct photolysis in aqueous solution by sunlight. The estimations from AOPWIN provide half-lives for the reactions of vapor phase 4-nitrophenol with photochemically generated hydroxyl radicals. The submitter needs to address this error.

RESPONSE: This section was modified to show the relative contributions of direct and indirect photolysis on PNP. The direct reaction of PNP is aqueous media with sunlight in expected to be an important consideration in the fate of PNP since it has such low volatility.

COMMENT 4: *Stability in water*. While EPA agrees that this chemical is stable to hydrolysis, the submitter needs to include this information in a robust summary. Furthermore, the submitter needs to indicate that 4-nitro-phenol does degrade in water upon exposure to sunlight, referencing the relevant data presented in the photodegradation section.

RESPONSE: The direct photodegradation information and reference were added.

COMMENT 5: *Biodegradation*. The submitter needs to provide a detailed description of each test including the OECD Screening test, and resolve other issues identified under the comments on the robust summaries.

RESPONSE:

This has been done. See response to "Comment 12"

COMMENT 6: *Fugacity*. The submitter used an incorrect vapor pressure in the input parameters. The correct value for 4-nitrophenol is 9.79x10-5 mmHg (see vapor pressure section, above). The submitter's Henry's law constant is not consistent with the experimental value cited in the PHYSPROP database, 4.15x-10 atm-m3/mole (Parsons et al. 1971). The submitter used half-lives in air, water, soil, and sediment that were very short, and did not explain why these were used. The submitter needs to address these vapor pressure, Henry's law constant, and half-life input issues.

RESPONSE: The correct values for the physical constants were used in a revised modeling exercise. The half-lives were revised based on the information that PNP is

clearly inherently biodegradable using revised conservative estimates considered representative of environmental conditions. The model was also run assuming release only to water as this is considered the most likely industrial situation. The information in the test plan was also modified accordingly.

COMMENT 7: *Repeated-dose toxicity*. The submitter needs to include in the robust summaries the 18-month chronic toxicity study in mice (NTP, 1994) discussed in the test plan.

RESPONSE:

A robust summary of this study has been added. As this is beyond the scope of the HPV screening and as it is a publicly available document, only a brief overview of the study design and results have been included in the robust summary.

COMMENT 8: *Genetic toxicity (gene mutation)*. The submitter needs to provide separate robust summaries for the Drosophila sex-linked recessive lethal assay (NTP, 1994) and the NTP's CHO-HGPRT forward mutation assay (Oberly et al, 1990), which are discussed as supporting data in the test plan.

RESPONSE:

These reports have been included in the robust summary of the Ames test as supporting studies with results and full references. We believe it is outside the scope of the HPV program guidelines to provide robust summaries for all supporting studies, especially those that are readily available in the open literature.

COMMENT 9: *Genetic toxicity (chromosomal aberration)*. The submitter needs to provide the SCE assay as a separate robust summary.

RESPONSE:

This report has been included in the robust summary of the chromosome aberration study as a supporting study with results and full references and a description of the major findings. We believe it is outside the scope of the HPV program guidelines to provide robust summaries for all supporting studies, especially those that are readily available in the open literature.

COMMENT 10: *Developmental toxicity*. The submitter needs to discuss the developmental toxicity criteria for the submitted 2-generation reproductive toxicity study. Since the study was conducted with much lower doses than those recommended by the OECD guidelines for the dermal route, and did not elicit any maternal toxicity at the

highest dose tested, the submitter needs to provide information on the selection of doses and exposure route.

The test plan and Tables 1 and 5 in the test plan need to specifically address the developmental toxicity endpoint.

RESPONSE:

An oral developmental toxicity in rats that shows clear maternal toxicity was inadvertently omitted from the initial submission. This study has been added as a separated robust summary. Administration by the oral route allowed a maternally toxic dose to be investigated relative to effects on the conceptus. In this study, high-dose pregnant dams showed both reductions in body weight and body weigh gain without any adverse effects on fetal parameters. Although this study has some deficiencies, it serves as the adequate developmental toxicity screening study required by the HPV program.

Information about this study has also been incorporated into the Test Plan in Table 1 and Table 5, and into a new section in the mammalian toxicity part of the plan.

Specific Comments on the Robust Summaries

COMMENT 11: Generic Comments: Some of the definitive values (e.g., EC50/LC50 and NOAELs/LOAELs) were reported as greater than or equal to ( ) in the respective fields. The submitter needs to remove the greater than (>) sign.

RESPONSE:

The "greater than" indication has been removed from the LOAELs and NOAELs

COMMENT 12: *Biodegradation*. (a) The submitter indicates that it used five OECD guideline 301 methods. However, the only tests that seem to follow OECD Guideline 301 are the Sturm test (301 B), the OECD Screen test (301 E), and the Closed Bottle test (301 D). This point needs clarification. (b) The Zahn-Wellens test is OECD Guideline 302 B for determining inherent biodegradability, not ready biodegradation as indicated in the robust summary. (c) The submitter needs to indicate clearly and accurately which tests provide inherent biodegradation results and which provide ready biodegradation results, rather than categorize them all as ready biodegradation. (d) The degradation time periods for the MITI test, the AFNOR test, and the Sturm test are missing.

RESPONSE:

A table of the biodegradation results giving the appropriate classification and some experimental details has been added to the test plan. The table provides a high degree of clarity about the individual tests but the question of the classification of PNP as readily

biodegradable cannot be unequivocally resolved. Discussion about this issue in included in the test plan.

The robust summary has been broken up into multiple robust summaries reflecting the various types of studies and outcomes. Because the article did not give a high-degree of detail about the conduct of each study, the guideline designation is left off where it cannot be assigned.

COMMENT 13: *Algae*. The submitter needs to provide the test concentrations used in the algal study.

RESPONSE:

The paper did not specifically give the concentrations used for each substance tested. Based on the dilution method given in the paper, the relevant concentrations of PNP in the concentration range of inhibition were calculated and added to the robust summary.

Environmental Defense Comments

COMMENT 14: The robust summary contains only a 2-generation reproductive study on NP administered via the dermal route. No developmental toxicity studies were reported. Since dermally-administered NP is not acutely toxic and no information was provided on the systemic levels of NP following dermal administration, the reproductive/ developmental dataset is inadequate for screening level purposes. We do note that no histological alterations of reproductive organs were detected in the oral or inhalation repeat dose studies, so a new reproductive toxicity study is not needed. However, an oral or inhalation developmental toxicity study is warranted, as data on this endpoint are not available.

RESPONSE:

We appreciate your thoughtful comments and have added a definitive oral developmental toxicity study that we found subsequent to the initial submission. The combination of the repeated-dose data and the developmental toxicity study indicate lack of reproductive toxicity potential. This conclusion is supported and supplemented by the dermal 2-genaration study.

Animal Protection Organizations Comments

No responses necessary

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

4-NITROPHENOL

CAS NO. 100-02-7

Revised March 25, 2004

Prepared by:

Solutia, Inc. Registration No.

575 Maryville Centre Drive,
St. Louis, Missouri 63141

EXECUTIVE SUMMARY

Solutia Inc. voluntarily submits the following revised screening information data and Test Plan covering the chemical, 4-Nitrophenol, also known as para-Nitrophenol or PNP (CAS No. 100-02-7), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with PNP. Use of key studies or estimation models available from data already developed provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing.

TABLE OF CONTENTS

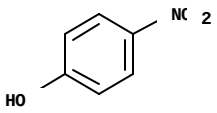
TEST PLAN FOR P-NITROPHENOL (PNP)

I. INTRODUCTION AND IDENTIFICATION OF THE CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Phenol, 4-nitro-, or PNP. The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of PNP, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature and fulfills Solutia's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of PNP and associated nomenclature.



Phenol, 4-nitro-

CAS No. 100-02-7
Synonyms: 4-Hydroxynitrobenzene; p-Nitrophenol; para-nitrophenol; PNP

B. Manufacturing & Use

Until the end of 2003, PNP was manufactured by a single US producer, Solutia Inc., at a single manufacturing site. That manufacturing site is now closed and Solutia is no longer a manufacturer or marketer of PNP. The manufacturing operation was a typical closed, continuous process. Only a few employees were involved in its manufacture and had minimal potential for skin or airborne exposure, which occurred chiefly during material transfer operations. Due to the high acute hazards associated with its potential to cause methemoglobinemia, specific manufacturing procedures and practices had been established to minimize the exposure potential to PNP.

p-Nitrophenol is sold to a limited number of customers at a few US processing sites and exported to ex-US sites for the express purpose of full chemical conversion into other industrial chemicals. As such, PNP is expected to chemically react to form chemicals used as dyes/pigments, pharmaceuticals, analgesics and adhesives. There are no known or suspected consumer exposures to PNP resulting from TSCA-related activities, as PNP is consumed as a chemical intermediate. Loss to the atmosphere or from non-POTW aqueous streams during manufacturing or processing is minimal. Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This initial assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with PNP. The data used to support this program include those Endpoints identified by the US EPA (1998a); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3.Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – This designation not used in this Dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. Additional studies have been identified during our literature search on the referenced HPV endpoints but have not been summarized in this Dossier. The reader is referred to three additional data compendia which also summarize available data on the physical-chemical properties, ecotoxicity, environmental fate and health effects of p-nitrophenol. These include the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000), the ECB IUCLID Dossier for p-Nitrophenol (2002), and the Hazardous Substances Data Bank (HSDB) (2002) for p-Nitrophenol.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Hence, no further testing for any of the HPV Endpoints is deemed necessary (Table 1).

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from reputable references and cited as an Accepted or Peer Reviewed value in the PNP Hazardous Substances Data Bank (2002) and/or IPCS CICAD on Mononitrophenols (2000). These endpoints have been classified as "2-Reliable with restrictions".

Environmental Distribution values for distribution in the environment (Fugacity) were obtained using a computer estimation –modeling program (EPIWIN, 2002) based on the EQC level III procedure recommended by EPA. These results have been classified as "2-Reliable with restrictions"

Environmental Fate. Biodegradation data for PNP and several other chemicals were summarized in a published article reporting results of multiple studies following the major biodegradation assessment protocols in use at the time. Since these studies followed established guidelines in an effort to compare and contrast results and since multiple compounds were also evaluated that can serve as positive and negative controls, the results are classified as "1-Reliable without restriction". Direct photodegradation data were obtained from a published study following EPA test guidelines and indirect photodegradation rates were estimated with the AOPWIN program was considered "2-Reliable with restrictions". In keeping with OECD SIDS guidance, no testing for Stability

in Water is planned with PNP as it is generally recognized as "stable" in aqueous solutions.

Ecotoxicity Endpoints were met with studies that were conducted according to OECD guidelines for Acute Invertebrate Toxicity (OECD 202) and Acute Plant Toxicity (OECD 201), or conducted according to study design and test parameters which preceded, but were consistent with OECD test guidance (Acute Fish Toxicity- OECD # 203). Studies supporting the Acute Invertebrate and Acute Plant Endpoints were designated a reliability level of "1-Reliable without restriction", while the Acute Fish study was designated "2-Reliable with restrictions", as it was well documented but conducted prior to inception of GLPs.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing, Reproductive Toxicity, and Developmental Toxicity) have all been filled by way of tests which either conformed directly with OECD test guidance or followed test designs similar to OECD guidance. The Acute Toxicity Endpoint was supported by a study which followed OECD guideline 401 and GLPs and was considered "1- Reliable without restriction". The Repeated Dose Toxicity Endpoint was met with an OECD guideline 408 study conducted in accordance with GLPs. It also was codified as "1- Reliable without restriction". Both the Ames test as well as an *in vitro* Chromosomal Aberration assay, used to support their respective Endpoints, were conducted by the US National Toxicology Program (NTP). The Ames test followed a study design equivalent to OECD guideline # 471 while the cytogenetics study was similar to, but not identical with, OECD guideline # 473. Thus, the Ames test was categorized as "1- Reliable without restriction" while the cytogenetics study was classified as "2- Reliable with restrictions".

Both a 2-Generation Reproduction Study and information from repeated-dose studies combined with information from a developmental toxicity study fulfills the HPV requirements for the Reproductive Toxicity Endpoint. The 2-genration study was conducted to meet US EPA pesticide guidance for reproductive toxicity both in design and GLP compliance. While it deviated slightly from OECD guideline # 416, it has been classified as "1- Reliable without restriction" since it has been accepted by EPA to fulfill the Reproductive Toxicity data requirement for pesticide reregistration purposes under FIFRA.

The Developmental study was designed to meet the requirement of FIFRA for pesticide re-registration. EPA, in their review of the study, noted that the study had deficiencies although they accepted to as fulfilling the rodent developmental toxicity endpoint for re-registration of PNP. It is assigned a reliability of 2 because it lacks details.

Following is a tabular depiction of data availability and testing recommendations for p-Nitrophenol (PNP).

Table 1. Test Plan Matrix for para-Nitrophenol (PNP)

	Information Available?	OECD?	GLP?	Other Study?	Estimation Method?	Acceptable?	Testing Recommeded ?
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	Y	N	Y	N
Boiling Point	Y	R	N	Y	N	Y	N
Vapor Pressure	Y	R	N	Y	N	Y	N
Partition Coefficient	Y	R	N	Y	N	Y	N
Water Solubility	Y	R	N	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	N	Y	Y	Y	N
Stability in Water	Y	N	N	N	Y	Y	N
Biodegradation	Y	Y	L	Y	N	Y	N
Distribution in Envir	Y	N	N	Y	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	N	Y	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	L	Y	N	Y	N
Toxicity to Aquatic Plants	Y	Y	L	Y	N	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	Y	Y	Y	N	Y	N
Repeated Dose Toxicity	Y	Y	Y	Y	N	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	Y	N	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	N	Y	Y	N-	Y	N
Reproductive Toxicity	Y	N	Y	N	N	Y	N
Developmental Toxicity	Y	N	Y	N	N	Y	N

Y = Yes; N = No; L = Likely, but not specified; R = Reputable Reference

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of para-Nitrophenol (PNP)

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 20 ^{o}C)	Water Solubility (mg/L)	Partition Coefficient (Log Kow)
p-Nitrophenol CAS No. 100-02-7	> 279 Degredation	114	0.00013	16,000 @ 25 ^{o}C.	1.91

All HPV Endpoints for Chemical/Physical Properties have been completed with reliable information and taken from either primary or reputable textbook references (Table 2). The values, which are included in the Robust Summary section of this Dossier, have been internationally accepted as accurately depicting the properties of PNP and are cited in the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000) and/or cited as peer-reviewed references in the Hazardous Substances Data Bank (HSDB, 2002). They have been classified as "2-Reliable with restrictions". Additional Chemical/Physical property values can also be found in the IPCS CICAD No. 20 (2000) and the ECB IUCLID Dossier for P-Nitrophenol (2002).

In summary, these data indicate that PNP is a solid at room temperature and has a low vapor pressure. It has a low octanol:water partition coefficient and is soluble in water.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

Extensive reviews and study citations in the Environmental studies area have been published on PNP, and are summarized in the IPCS CICAD (2000), in the HSDB (2002) and in the ECB IUCLID Dossier (2002) for PNP. Key studies have been selected for this Dossier, which fairly depict the consensus conclusion/values for each of the HPV Endpoints, and are summarized in the Robust Summary section of this Dossier.

Several tests of biodegradation have been conducted with PNP. The most informative information was generated by Gerike and Fisher (1979) who presented biodegradation data for PNP from 9 studies run with the same test material and in some studies the same biochemical inoculum. Numerous other compounds were also studied for the purpose of comparing the major guideline testing protocols for biodegradation assessment. Among these 9 protocols were 7 that are used to assess "ready" biodegradation and two that are considered tests of inherent biodegradation. The list of tests and classifications are shown in Table 3A along with the results.

Table 3A Biodegradation Results for para-Nitrophenol (PNP)

Type	Test	Conc. (mg C/L)	Time (days)	O_2 Uptake or CO_2 evol (%)	DOC Removal (%)	Result
Ready	Closed Bottle test	1	30	0		Fail
	Modified Closed Bottle Test*	1	30	60		Equivocal
	OECD Screening Test	3-20	19		100	Pass
	Sturm Test	10	28	90		Pass
	Modified Sturm Test**	10	42		98	Pass
	ANFOR Test	40	42		97	Pass
	MITI Test (German mixed inoculum)	50	14		1	Fail
Inherent	Zahn-Wellens Test	400	10		92	Pass
	Coupled Units Test	>12	7		100	Pass

* Includes additional trace elements and vitamins
** Includes an acclimation period.

These results are also confirmed by additional MITI tests, a SCAS test and a few other non-guideline studies that gave results similar to those in the table (IPCD, 2000). Taking the results in toto, leads one to conclude that PNP is undoubtedly classified as "inherently biodegradable" and would also be classified as "readily biodegradable" on the basis of the OECD Screening test, the Sturm test or the ANFOR test if these were all that were available. Although absolute classification as readily biodegradable might be tenuous in light of the "failed" studies, what can be inferred from these data is that PNP is not resistant to biodegradation but probably requires some degree of bacterial adaptation to efficiently be biodegraded. It can be concluded that PNP will have a short half-life in waters where the microflora are commonly exposed to PNP and that introduction of PNP into a non-acclimated aquatic environment will still result in effective biodegradation but the process will be slower.

The molecular structure of PNP possesses only 2 functional groups (aromatic nitro and phenol), both of which are listed as types of Organic Functional Groups that are Generally Resistant to Hydrolysis (Table 7.1, Lyman et al, 1990). PNP is also considered "stable" in water by the German Umweltbundesamt, based on tests conducted in Germany (Schmidt-Bleek et al, 1982). PNP hydrolysis has also been reported as "nil" at pH 2, pH 7 and pH 12 (Capel and Larson, 1995). Photochemical degradation of PNP in an aquatic system has been evaluated in "the EPA Test" using the methodology of Leifer and Stern (Hustert et al, 1981). Estimation of Transport (Fugacity) was made using an EPA-accepted estimation model (EPIWIN, 2002). These values have been designated as "2-Reliable with restrictions". An overview of the known qualities of the environmental properties of PNP is provided below.

The Environmental Fate of PNP can be summarized, as follows. Upon release to the air in the vapor state, PNP would be degraded in the atmosphere by reaction with photo chemically-produced hydroxyl radicals; the half-life for this reaction in air is approximately 6 days (Table 3B - Photodegradation). PNP, however will adsorb to particles. Thus, as PNP is mostly particle-bound in the atmosphere; its availability for photochemical reaction is limited (IPCS, 2000). Significant volatilization from soil or water to air is not expected, based on its vapor pressure (Table 2) and Henry's Law constant, respectively (IPCS, 2000). Atmospheric PNP, bound to particles, is expected to wash out to surface waters and soils by dry and wet deposition. Fugacity modeling (Table 3B) indicates that PNP released to water will distribute less than 1% to sediment and negligible amounts will distribute to air or soil. In aqueous solution, PNP appears stable (Table 3B-Stability in Water). PNP has been classified as possessing low to moderate potential for soil sorption and can be decomposed under aerobic conditions, Microbial decomposition can occur in different environmental compartments after adaptation of the microflora. Experimental results from bioaccumulation studies (IPCS, 2000; ECB IUCLID, 2002) indicate PNP has a low potential for bioaccumulation.

Table 3B. Environmental Fate and Biodegradation Parameters for para-Nitrophenol (PNP)

Chemical	Biodegradation	Stability in Water	Fugacity %	Photodegradation Rate (T1/2), days
p-Nitrophenol CAS No. 100-02-7	See Table 3A	Stable	Air – 7.18E-08 Water – 99.8 Soil – 1.77E-4 Sediment – 0.187	Indirect (atmospheric) 2.5 Direct (water): 5.7 (pH 5) 6.7 (pH 7) 13.7 (pH9)

Conclusion – Adequate studies following either OECD or EPA test guidance are available to provide needed information regarding the Biodegradation and Photodegradation of PNP. Information on Transport (Fugacity) was derived using the EQC Level III model in EPIWIN, an accepted estimation-modeling program. As PNP possesses only functional groups generally known to be resistant to hydrolysis, testing for stability in water is not needed (SIDS Manual-new draft version). Therefore, no additional data development is warranted for these HPV Endpoints.

C. Aquatic Toxicity

The aquatic toxicity of PNP has been extensively reviewed (IPCS, 2000; HSDB, 2002; ECB IUCLID, 2002) and contains both acute and chronic toxicity studies on algae, invertebrates and fish. Studies selected for development of Robust Summaries are reported in Table 4 and depict the level of toxicity generally observed for these Endpoints within the overall dataset.

Both the Acute Invertebrate and the Acute Algae studies were conducted according to OECD test guidance # 202 and 201, respectively. While no mention was made of GLP compliance in the referenced publications, it is reasonable to assume both were conducted under GLP auspices as they followed OECD method guidance and were conducted to meet national regulatory mandates. Thus, both studies are considered "1- Reliable without restriction". The Acute Fish Toxicity study was conducted prior to inception of OECD/GLP guidance but is considered well documented and used methodology consistent with OECD guidance for this study type. This study is considered "2- Reliable with restrictions" only because it was conducted prior to codification of testing and GLP guidelines.

Table 4. Aquatic toxicity parameters for para-Nitrophenol (PNP)

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
p-Nitrophenol CAS No. 100-02-7	5.8 (bluegill-96 hr)	22.0 (Daphnia-48 hr)	32.0 (96-hrs)

PNP is considered to be "Slightly Toxic" toward these and other aquatic species following acute testing (IPCS, 2000). Based on the pattern and release scenarios envisioned, PNP is expected to present a negligible risk to aquatic organisms.

Conclusion – Adequate studies which meet internationally accepted test guidelines are available on all 3 Aquatic Toxicity Endpoints to assess the acute aquatic toxic hazards associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

Table 5. Mammalian Toxicity of p-Nitrophenol (PNP)

Chemical Name/ CAS no.	Acute Toxicity		Repeat Dose Toxicity			Reprotoxicity	Developmental	Mutagenicity – In Vitro	
	OLD50 (rat)	DLD50 (rabbit)	90-day	28-day	Chronic	2-Gen.	Gd 6-16	Ames	Chrom. Aberr.
p-Nitro-phenol 100-02-7	230 mg/kg	> 5000 mg/kg	(oral-rat) NOEL 25 mg/kg/d	(inhal-rat) NOEL 5 mg/m3	(dermal-mouse) NOEL (systemic tox./carc.) 160 mg/kg/d	(dermal-rat) NOEL (maternal-systemic) 250 mg/kg/d NOEL (reprotox) 250 mg/kg/d	(oral –rat) NOEL (Maternal) 13.8 mg/kg-day NOEL (Developmental) 127.6 mg/kg-day	Neg.- All strains +/- S9	Neg. (- S9) Pos. (+S9)

1.0 Acute Toxicity

Results of acute toxicity studies by both the oral and dermal routes of exposure have been conducted as summarized in Table 5. Both studies were conducted using study designs consistent with OECD Test Guidelines 401 and 402, respectively, under auspices of GLPs, and are deemed "1- Reliable without restriction". The acute rat oral toxicity study has been chosen as the key study to fulfill this HPV Endpoint. The acute rabbit dermal toxicity study is included as Supplemental information.

PNP is considered to be moderately toxic after acute oral exposure to rats. As there were no deaths or untoward signs of toxicity after acute dermal exposure well above generally accepted Limit Dose levels (1,000 mg/kg), PNP is considered practically non-toxic after acute dermal exposure to rabbits. However, based on the ability of PNP to produce methemoglobinemia in humans, this material is considered to be toxic in the workplace

by all acute exposure routes. Additional acute toxicity values in animals can be found listed in the three compendium reports cited above.

Conclusion – A quality study, compliant with OECD/GLP guidance, is available to assess the Acute hazards associated with PNP. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

PNP has been adequately tested by several routes of exposure to define its Repeated Dose Toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route. This study was conducted using a study design consistent with OECD Test Guideline 408, and under GLP auspices and is considered "1- Reliable without restriction". Early deaths related to PNP acute toxicity, and exacerbated by repeat dosing, occurred at dosage levels of 70 and 140 mg/kg-day. No other treatment-specific effects or organ pathology, including involvement of male and female gonads (i.e. testes and ovaries), were reported. A NOEL of 25 mg/kg-day was established. A summary of this study and a 4-week Range Find study are found in the Robust Summary section of this Dossier. The IPCS CICAD (2000) also summarizes a 28-day oral gavage study (Andrae et al. 1981) with PNP at substantively higher levels, which resulted in excessive toxicity. This study was not considered in this review as it is not available in English and is superceded by the current study, which is of longer exposure duration by the same route and has utilized a more appropriate selection of doses.

PNP also has been tested following inhalation exposure (Table 5). This study was not selected for inclusion as the key Repeated Dose Study, as it was conducted for a shorter (4-weeks) time period than the 90-day study referenced above. However, it too is considered "1- Reliable without restriction" and is included in the Robust Summary section of this Dossier.

It should be noted that no evidence of effects on the gonads was seen in either sex of rat in the studies cited above. Further, results of an 18-month chronic toxicity study in male and female mice (NTP, 1994) also cited in Table 5, resulted in no organ-related toxicity, including the gonads, up to the highest level tested (160 mg/kg-day, 3x/wk, 78 wks).

Conclusion - Thus, the Repeated Dose HPV Endpoint for PNP has been fulfilled with a 90-Day Subchronic study in rats deemed "1- Reliable without restriction". No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

3.1 Mutagenicity Testing (Ames test)

PNP has been extensively tested in the standard Ames assay for point mutations (ECB IUCLID, 2002; IPCS CICAD, 2000). PNP elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. The Haworth et al, (1983) study, conducted on behalf of the NCI/NTP program, has been summarized in the Robust Summary section of this Dossier and its results are referenced in Table 5. Its design and documentation are such that it is considered equivalent to OECD guideline # 471 and thus is "1- Reliable without restriction" for this assessment. Additionally, PNP has been tested in the secondary tier *Drosophila* Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program (NTP, 1994). Oberly et al, 1990 reported that PNP elicited no mutagenic activity when tested in a CHO-HGPRT forward mutation assay in mammalian cells.

Thus, it is concluded that adequate testing of sufficient quality has been performed on PNP to evaluate the Ames Test (Point Mutation) HPV Endpoint; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

As part of the NCI/NTP program (Galloway et al 1987), PNP was tested in the CHO cell *in vitro* assay to determine its capacity to induce chromosomal aberrations. A Robust Summary has been prepared for this study and its results are referenced in Table 5. PNP was negative for structural chromosome damage up to severely cytotoxic concentrations (>750 ì g/ml) in a metabolic activation system-free environment. It did produce reproducible, dose-related and statistically significant increases in cells with structural chromosomal aberrations at levels of 1500 and 1700 ì g/ml PNP after metabolic activation, although cells at these levels had undergone severe cell cycle delay. The quality of this study is considered to be "2- Reliable with restrictions", as it did not follow an established OECD protocol, yet was well documented and has been used for regulatory purposes. In a corresponding Sister Chromatid Exchange (SCE) assay conducted in the same CHO cell test (Galloway et al. 1987), PNP produced no SCEs up to doses that caused severe cell cycle delay (25 ug/ml without S9 and 1700 ì g/ml with S9).

The HPV Chromosomal Aberration Endpoint for testing of PNP has been fulfilled with adequately conducted and documented studies and no further testing is needed.

4.0 Reproductive Toxicity

A Two-Generation rat Reproduction Toxicity study of dermally applied PNP has been conducted (Table 5) and summarized in Dossier section VI - Robust Summaries. This

study is considered adequate for assessment of this Endpoint as it has been accepted as such by IPCS (2000) and was judged "adequate" for US EPA pesticide reregistration (US EPA, 1998b). It was conducted under GLPs and followed OPPTS testing guidelines. Based on general acknowledgement of its scientific and regulatory acceptability, it has been judged as "1- Reliable without restriction" for purposes of this assessment. PNP was administered dermally in ethanol to groups of 12 male and 24 female rats at 50, 100 and 250 mg/kg/d. No indication of systemic toxicity was observed in either parental generation, although dermal irritation was observed at the site of application. No reproductive toxicity was observed at any dose tested in either the F1 or F2 matings. Both the adult systemic and reproductive toxicity NOELs are considered to be the highest dosage tested, i.e. 250 mg/kg/d.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled with conduct of a Two-generation rat study which followed regulatory testing guidance, was conducted under GLPs, and accepted in support of pesticide reregistration. Thus, no further testing for this HPV Endpoint is required.

5.0 Developmental Toxicity

A developmental toxicity study of orally (gavage) administered PNP has been conducted (Table 5) and summarized in Dossier section VI - Robust Summaries. This study is considered adequate for assessment of this Endpoint as it has been by the US EPA pesticide re-registration (US EPA, 1998b). Based on general acknowledgement of its scientific and regulatory acceptability, it has been judged as "1- Reliable without restriction" for purposes of this assessment. PNP, in propylene glycol solution, was administered by gavage to 20 pre-mated female Sprague-Dawley rats at dose levels of 0, 1.4, 13.8 or 27.6 mg/kg/day from days 6 through 16 of gestation. Rats were sacrificed prior to delivery and the products of conception were examined for viability, morphology and other standard fetal parameters. Decreased maternal body weight (12%) and body weight gain (45%) were observed during the dosing period at the high-dose level of 27.6 mg/kg-day. Treatment-related effects on mortality, clinical signs, food consumption or cesarean parameters were not reported. Food consumption was not measured. Based on decreased body weight and body weight gain the maternal LOEL is judged to be 27.6 mg/kg-day. The maternal NOEL was found to be 13.8 mg/kg/day. The developmental NOEL was found to be 27.6 mg/kg-day and a developmental LOAEL was not found. (US EPA, 1998b). Thus, PNP is judged not to be a specific developmental toxin.

One issue of potential concern is materials that produce significant methemoglobanemia can restrict oxygen delivery to the conceptus. PNP has very weak methemoglobin producing capability (ICPS, 2000); therefore, this concern is reduced.

In conclusion, the Developmental Toxicity HPV endpoint has been fulfilled with a study considered adequate for assessment of this endpoint. Thus, no further testing for this HPV endpoint is required.

V. REFERENCES

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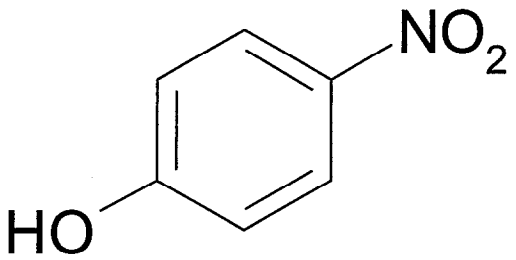
VI. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are appended

p-Nitrophenol (CASNO 100-02-7)



U.S. EPA HPV

Data Set

Existing Chemical	:	ID: 100-02-7
CAS No.	:	100-02-7
EINECS Name	:	4-nitrophenol
EC No.	:	202-811-7
TSCA Name	:	Phenol, 4-nitro-
Molecular Formula	:	C6H5NO3

Producer related part

Company	:	Solutia Inc
Creation date	:	10.02.2004

Substance related part

Company	:	Toxicology and Regulatory Affairs
Creation date	:	10.02.2004
Status	:	
Memo	:	Revised Robust Summaries
Printing date	:	29.02.2004
Revision date	:	
Date of last update	:	29.02.2004
Number of pages	:	29

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Solutia Inc
Contact person	:	
Date	:	
Street	:	
Town	:	
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Remark	:	Updated February 2004 by Elmer Rauckman PhD DABT Toxicology and Regulatory Affairs Freeburg, IL rauckman@toxicsolutions.com

29.02.2004

1.2 SYNONYMS AND TRADENAMES

2.1 MELTING POINT

Value	:	= 114 °C
Sublimation	:	
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol; also cited as a definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (4)

2.2 BOILING POINT

Value	:	> 279 °C at
Decomposition	:	Yes
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	no data
Test substance	:	p-Nitrophenol CASNO 100-02-7
Reliability	:	(2) valid with restrictions Handbook values are assigned a reliability score of 2
Flag	:	Critical study for SIDS endpoint

24.10.2002 (13)

2.4 VAPOUR PRESSURE

Value	:	= .00013 hPa at 20 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Vapor pressure converted to hPa from original extrapolated 20 deg value of 1.27 exp -7 Atm.
Test substance	:	p-Nitrophenol CASNO 100-02-7
Reliability	:	(2) valid with restrictions Data obtained by a scientifically defensible method.
Flag	:	Critical study for SIDS endpoint

19.02.2004 (16)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	<= 1.91 at °C
pH value	:	
Method	:	other (calculated)
Year	:	1985
GLP	:	no data
Test substance	:	no data
Source	:	Solutia Inc. St. Louis
Reliability	:	(2) valid with restrictions Value of <2.4 cited as definitive value in IPCS CIDAD Document 20 - Mononitrophenols (2000).
Flag	:	Critical study for SIDS endpoint

24.10.2002 (8)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	
Value	:	= 16000 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other
Year	:	1996
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (23)

3.1.1 PHOTODEGRADATION

Type	:	other: Air and water
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Spectrum of substance	:	lambda (max, >295nm) : 290 nm epsilon (max) : epsilon (295) :
Conc. of substance	:	10 mol/l at °C
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 6.7 day(s)
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000
Rate constant	:	= .0000000000043 cm^3/(molecule*sec)
Degradation	:	= 50 % after 2.5 hour(s)
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	

Method :

DIRECT:
Dissolved in deionized water (1.18 g/100 ml) to which was added an acetate, phosphate or borate component to bring solution to pH 5, 7 or 9, respectively and introduced to sunlight (blind controls used). Analysis performed by GC using EC detector.

INDIRECT:
The indirect photolysis rate and half-life were estimated using the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN ver 1.90) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. This program uses structural features of the molecule to estimate and sum the individual contribution of each hydrogen atom to arrive at a reaction-rate constant for hydrogen abstraction by atmospheric hydroxyl radical. It also estimates the rate constant for the gas-phase reaction between ozone and olefinic or acetylenic compounds. The rate constants estimated by the program are then used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radicals and ozone.

Remark :

The directphotolysis estimate is based on aqueous solutions in direct sunlight and although the half-life is longer than for atmospheric material it can be an important mechanism for PNP loss because PNP has such low volatility/

Result :

The following results are from APOWIN based on the structure of the molecule

```
AOP Program (v1.90) Results:
============================
SMILES : c1cc(O)ccc1N(=O)(=O)
CHEM   :
MOL FOR: C6 H5 N1 O3
MOL WT : 139.11
----- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
----
Hydrogen Abstraction       =   0.0000 E-12
cm3/molecule-sec
Reaction with N, S and -OH =   0.1400 E-12
cm3/molecule-sec
Addition to Triple Bonds   =   0.0000 E-12
cm3/molecule-sec
Addition to Olefinic Bonds =   0.0000 E-12
cm3/molecule-sec
Addition to Aromatic Rings =   4.1652 E-12
cm3/molecule-sec
Addition to Fused Rings    =   0.0000 E-12
cm3/molecule-sec

   OVERALL OH Rate Constant =   4.3052 E-12
cm3/molecule-sec
   HALF-LIFE =     2.484 Days (12-hr day; 1.5E6 OH/cm3)
   HALF-LIFE =    29.813 Hrs

---- SUMMARY (AOP v1.90): OZONE REACTION --------------
----

       ******  NO OZONE REACTION ESTIMATION ******
       (ONLY Olefins and Acetylenes are Estimated)

 NOTE: Reaction with Nitrate Radicals May Be Important

Experimental Database:  NO Structure Matches
```

Test substance :
p-Nitrophenol CASNO 100-02-7

Conclusion :
Indirect photolysis in atmosphere: Half-life = 2.5 days

Direct photolysis in water: Half-life of 5.7 days at pH of 5, 6.7 days at pH of 7 and 13.7 days at pH 9.

Reliability : (2) valid with restrictions
Estimates based on EPIWIN are assigned a reliability of 2.

Flag : Critical study for SIDS endpoint
20.02.2004 (3) (11)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Degradation : < 50 % after 1 year at pH and °C

Method :

The water stability of this material may be reliably estimated from chemical principles. Aromatic nitro groups and hydroxyl groups are listed as functional groups that are generally resistant to aqueous hydrolysis at environmental pH levels (Harris 1990).

In addition to hydrolytic stability the effect of sunlight on environmental fate in surface waters is a factor needs to be considered for this compound. Hustert, et al (1981) determined the effect of natural sunlight on PNP in water at three different pH values. They found that sunlight exposure caused loss of PNP with a half-life of about a week (please see the accompanying robust summary on photodegradation for details)

(Hustert, K,, Mansour, M, Parlar, H and Korte, F. 1981. Der EPA-Test - Eine methode zur bestimmung des photochemischen abbaus von organischen verbindungen in aquatischen systemen. Chemosphere 10 (9):995-998.)

Result :

The knowledge that the functional groups in PNP are not susceptible to hydrolysis allows prediction of a half-life > 1 year for PNP in the absence of significant exposure to direct sunlight. In situations where the compound is exposed to direct sunlight by presence in the first few cm of surface water, the half-life will be shorter proportionally to the sunlight exposure.

Test substance :

p-Nitrophenol CASNO 100-02-7

Conclusion :

The hydrolysis half-life of PNP at ambient temperatures and typical environmental pH levels is greater than one year. Exposure of PNP containing surface water to direct sunlight will cause loss of PNP with a half-life of about a week.

Reliability : (2) valid with restrictions

A reliability code of 2 is assigned to values obtained from reliable estimation methods.

Flag : Critical study for SIDS endpoint

19.02.2004 (9)

3.3.2 DISTRIBUTION

Media : other: air, water, soil, sediment
Method : Calculation according Mackay, Level III
Year : 2004

Method :

Measured values for physical values of PNP were input into EPIWIN as shown below. Biodegradation rates were estimated from experimental results showing inherent biodegradability. Model was set to assume initial distribution to water only as this is the most likely industrial situation. EQC Level III model (as found in EPIWIN 3.05) was utilized.

Result : Results of the Level III fugacity modeling are:

```
Level III Fugacity Model (Full-Output):
=======================================
  Chem Name   : 4-Nitrophenol
  Molecular Wt: 139.11
  Henry's LC  : 4.15e-010 atm-m3/mole (user-entered)
  Vapor Press : 9.79e-005 mm Hg  (user-entered)
  Liquid VP   : 0.000743 mm Hg  (super-cooled)
  Melting Pt  : 114 deg C (user-entered)
  Log Kow     : 1.91  (user-entered)
  Soil Koc    : 33.3  (calc by model)

          Concentration   Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       7.18e-008       55          0
   Water     99.8            360         1000
   Soil      0.000177        360         0
   Sediment  0.187           500         0

          Fugacity   Reaction  Advection  Reaction
Advection
           (atm)     (kg/hr)   (kg/hr)   (percent)
(percent)
Air       4.31e-019   3.09e-6   2.46e-6   3.09e-7
2.46e-007
Water     5.09e-015   658       342       65.8
34.2
Soil      9.1e-020    0.00116   0         0.000116   0
Sediment  2.65e-015   0.886     0.0128    0.0886
0.00128

   Persistence Time: 342 hr
   Reaction Time:    520 hr
   Advection Time:   1e+003 hr
   Percent Reacted:  65.8
   Percent Advected: 34.2

   Half-Lives (hr), (based upon user-entry):
      Air:      55
      Water:    360
      Soil:     360
      Sediment: 500

   Advection Times (hr):
      Air:      100
      Water:    1000
      Sediment: 5e+004
```

Test substance :

p-Nitrophenol CASNO 100-02-7

Conclusion :

Under conditions of initial distribution to water, PNP is expected to remain almost exclusively in the water compartment with less than 0.2% predicted to distribute to sediment.

Reliability : (2) valid with restrictions

A reliability code of 2 is assigned to values obtained from reliable estimation methods.

Flag : Critical study for SIDS endpoint

19.02.2004 (14)

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Concentration : 1 mg/l related to DOC (Dissolved Organic Carbon)

Contact time : 30 day(s)
Degradation : = 0 % after 30 day(s)
Result : under test conditions no biodegradation observed

Method :

Closed bottle test, after OECD 301D

Test substance :

p-Nitrophenol CASNO 100-02-7

Reliability : (2) valid with restrictions

Details lacking.

Flag : Critical study for SIDS endpoint

29.02.2004 (6)

Type : aerobic
Inoculum :
Concentration : 50 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time : 14 day(s)
Degradation : 1 % after 14 day(s)
Result : under test conditions no biodegradation observed

Method :

Followed MITI protocol except innoculum collected from several sites in the area of the laboratory.

Test substance :

p-Nitrophenol CASNO 100-02-7

Reliability : (2) valid with restrictions

Details lacking

29.02.2004 (6)

Type : aerobic
Inoculum :
Concentration : 1 mg/l related to DOC (Dissolved Organic Carbon) related to

Contact time	:	30 day(s)
Degradation	:	= 60 % after 30 day(s)
Result	:	other: limited biodegredation under conditions
Method	:	Modified closed bottle test, similar to OECD 301D
Remark	:	Modified conditions included some trace matals and vitamins added to medium.
Test substance	:	p-Nitrophenol CASNO 100-02-7
Reliability	:	(2) valid with restrictions Details lacking.

29.02.2004 (6)

Type	:	aerobic
Inoculum	:	
Concentration	:	10 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	28 day(s)
Degradation	:	90 % after 28 day(s)
Result	:	inherently biodegradable
Method	:	Used standard Sturm test procedure as described by Sturm (1973) with carbon dioxide evolution as the measured indicator of biodegradation.
Remark	:	Standard Sturm test
Test substance	:	p-Nitrophenol CASNO 100-02-7
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

29.02.2004 (6)

Type	:	aerobic
Inoculum	:	
Concentration	:	400 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	10 day(s)
Degradation	:	92 % after 10 day(s)
Result	:	inherently biodegradable
Method	:	Followed procedure of Zahn and Wellens except that only DOC was measured.
Test substance	:	p-Nitrophenol CASNO 100-02-7
Reliability	:	(2) valid with restrictions Details lacking

29.02.2004 (6)

Type : aerobic
Inoculum :
Concentration : 40 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time : 42 day(s)
Degradation : 97 % after 42 day(s)
Result : readily biodegradable

Method :
Standard French norm procedure (ANFOR)
Test substance :
p-Nitrophenol CASNO 100-02-7
Reliability : (2) valid with restrictions

Details lacking
29.02.2004 (6)

Type : aerobic
Inoculum :
Contact time : 19 day(s)
Degradation : 100 % after 19 day(s)
Result : readily biodegradable

Method :
Modeled after OECD sceeening test except some trace minerals and viatamins were added to enhance bacterial activity. Prodedure modified to use DOC analysis as measured parameter. COncentration 20 or 10 mg C/L.
Test substance :
p-Nitrophenol CASNO 100-02-7
Reliability : (2) valid with restrictions

Details lacking
29.02.2004 (6)

Type : aerobic
Inoculum :
Concentration : 10 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time : 42 day(s)
Degradation : 100 % after 42 day(s)
Result :

Method :
Modified Sturm test with preacclimation procedure with 20 mg/l test material. Prodedure modified to use DOC for measurement.
Remark :
Modified Sturm test
Test substance :
p-Nitrophenol CASNO 100-02-7
Reliability : (2) valid with restrictions

Details lacking

29.02.2004 (6)

Type	:	aerobic
Inoculum	:	
Concentration	:	12 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	7 day(s)
Degradation	:	100 % after 7 day(s)
Result	:	
Method	:	Standard coupled-units procedure usind DOC removal as parameter.
Test substance	:	p-Nitrophenol CASNO 100-02-7
Reliability	:	(2) valid with restrictions

Details lacking

29.02.2004 (6)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	>= 5.8 calculated
Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	other TS
Method	:	This study preceeded development of OECD Test Guideline 203 but was conducted in a manner consistent with that guideline. Groups of bluegill fingerlings (mean length of 2.8 cm); fish were not fed 48 h prior to nor during the 96 hr exposure period. Groups of 10 fish were added to glass vessels containing 15 l water at 5 test concentrations (8.7, 5.6, 3.7, 2.4 and 1.6 mg/L PNP) dissolved in acetone. Both a negative control and an acetone-containing control group were also used. No aeration was performed during the test. Water temperature was maintained at 22+/-1%, with a pH ranging between 6.7-6.3. Dissolved oxygen ranged from 93% saturation at study start to 7% at study termination. Observations and mortality were checked every 24 hr. At the end of the study, test concentrations and observed mortality were converted to logarithms and probits, respectively, and analyzed by a least square regression method for determination of LC50 and CI at 24, 48, and 96 hr timepoints.
Result	:	All deaths occurred during the first 24 hr of the study, hence the LC50 and CI values for each of the study time points (24, 48, 96 hr) were the same, i.e. LC50 = 5.8 (3.7-9.2) mg/L. Mortality (%) observed at each concentration was: 100% @ 8.7mg/L, 10% @ 5.6 mg/L, and 0% @ 3.7 mg/L, 2.4 mg/L, 1.6 mg/L, untreated control and acetone control.
Test substance	:	Purity of 99%.
Reliability	:	(2) valid with restrictions This study was conducted prior to, but consistent with OECD Guideline # 203 and, US GLP guidelines effective in 1979 for nonclinical laboratory studies.Reduction in oxygen over time is not considered a factor in interpretation of results since all deaths (10%) occurred within first 24 hrs of study.
Flag	:	Critical study for SIDS endpoint

29.02.2004 (17)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static

Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
NOEC	:	= 13 measured/nominal
EC50	:	>= 22 calculated
Analytical monitoring	:	no
Method	:	OECD Guide-line 202
Year	:	1980
GLP	:	no data
Test substance	:	other TS

Method : Methods used followed protocol as found in US EPA,1975 for Macroinvertebrate testing, which are consistent with OECD Guideline 202. D. magna, <24h old, were used as the tester strain. Culture water was reconstituted as outlined in US EPA, 1975 guidance, such that it contained a total hardness of 173+/-13 mg/l as CaCO3 and a pH of 8.0+/-0.2. Temperature was maintained at 22+/-1 degree C. A stock solution of the chemical in distilled water was prepared and used to provide a series of graded concentrations (reportedly 5-8) for testing. PNP was added to 500 mL diluent water in 2-L jars to prepare for each test solution. The 500 mL volume of test solution was divided into three 150-mL aliquots to provide triplicate exposures at each concentration. Five Daphnids were randomly placed in each test solution within 30 min of preparation. A negative control was also tested. Meaurements were taken to confirm dissolved oxygen concentration, pH, and temperature in the high, medium and low test concentrations. Observations were made at 24 and 48 hours of exposure and any mortalities were recorded. Mortality data were used to calculate an LC50 and CI using a moving average angle method.

Result :

LC50 (CI) values for 24 hr and 48 hrs were, respectively, 24 (22-26) mg/L and 22 (20-24) mg/L. ; The No Discernable Effect level was 13 mg/L. Dissolved oxygen concentrations ranged from 6.5-9.1 mg/L, pH values measured 7.4-9.4 units.

Test substance : Test compound purchased from commercial chemical supplier, hence technical grade PNP was likely used and had purity of 99%.

Reliability : (1) valid without restriction
GLP compliance was not stated in the article but adequate documentation can be assumed as this study was performed for the US EPA under contract no. 68-01-4646.

Flag : Critical study for SIDS endpoint

29.02.2004 (12)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC10	:	>= 8 calculated
EC50	:	>= 32 calculated
Limit test	:	

Analytical monitoring	:	no
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	
GLP	:	no data
Test substance	:	other TS
Method	:	Following test guidelines set by OECD, 1983 and German Umweltbundesamt, 1982. Experiments were incubated at 22+/-2 degrees C. at constant photosynthetically effective light intensity. Due to a distinct change of pH value caused by inclusion of PNP in sterilized double distilled water used as the diluent in this study, the pH of the stock solution was adjusted to pH 7 using NaOH. Experiments were performed by preparing two parallel dilution series in 300-ml Erlenmeyer flasks containing a saturated test chemical solution, medium and 5 ml algae suspension of approx. 10E4 cells/ml. Each Erlenmeyer flask was shaken 2-3 times per day and continuously illuminated from the side by two fluorescent lamps. After 0, 72 and 96 hrs, the cell growth of a 10-mm layer of cell suspensions from each test culture and from the controls was measured at 578 nm using a spectrophotometer. The extinction units were converted to cell numbers using a standard curve and the cell numbers determined using the Utermoehl method. The concentration-effect relationships were plotted on semilogarithmic paper and EC10 and EC50 values determined graphically. Concentrations of test material were determined based on its water solubility and a 2-fold dilution approach to which algal cells were added. The calculated relevant concentrations are 4.8, 9.6, 19.2, 32.4, 76.8 and 153.6 mg/L. These are not specifically given in the paper but were calculated in response to a request by EPA for concentrations.
Test substance	:	Commercial grade PNP, and thus with purity of 99%.
Reliability	:	(1) valid without restriction While not explicitly stated, the fact that this study was conducted according to national (Ger) and international (OECD) test guidelines it most likely was conducted consistent with or actually followed GLP guidance.
Flag	:	Critical study for SIDS endpoint

29.02.2004 (7)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 230 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	50
Vehicle	:	other
Doses	:	
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Administered by gavage using propylene glycol as vehicle to 5 groups of rats (5 male and 5 female) given 70, 110, 171, 268 or 420 mg/kg/d; Clinical signs recorded 3X during first 8-hr after dosing and 2X daily for the remainder of the 14-d observation period. Body weights recorded on test days 0, 7 and 14. All survivors were necropsied on test day 15. Food and water administered ad libitum. LD50 and CI determined using method of Finney, DJ. 1971. Probit Analysis, Cambridge Univer. Press.
Result	:	LD50 +/- Confidence Limits (95%): 230 mg/kg (182-289 mg/kg); Deaths: 70 mg/kg (0/10), 110 mg/kg (0/10), 171 mg/kg (3/10), 268 mg/kg (8/10) and 420 mg/kg (8/10); Deaths all occurred within the first 8 hrs of dosing and exhibited the following clinical signs: convulsions, prostration and dyspnea prior to death; Clinical signs observed in survivors during the first three days after dosing included: tremors, ptosis, salivation and lethargy. No untoward effects were noted at necropsy of survivors.
Test substance	:	Technical grade purity of > 99%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

29.02.2004 (21)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Value	:	> 5000 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	physiol. saline
Doses	:	
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1983
GLP	:	yes

Test substance	:	other TS
Method	:	One group of 5 male and 5 female rabbits were administered 5000 mg/kg/d test material on the shaved and abraded dermal surface. After administration the site was occluded and test material left in place for 24 hours. After test material removal, animals were observed for the remainder of the 14-d observation period. Clinical signs were recorded 3X during the first 8 hrs and 2X daily for the remainder of the study. Body weights were recorded on test days 0, 7 and 14. Necropsies were performed on all animals on test day 15. Food and water were administered ad libitum.
Result	:	No deaths occurred and no signs of systemic toxicity were seen during the study or at necropsy. Erythema and edema were observed during visual observations and at necropsy.
Test substance	:	Technical grade purity of > 99%
Reliability	:	(1) valid without restriction

29.02.2004 (22)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	Once daily throughout the exposure period
Post exposure period	:	None
Doses	:	0, 25, 70 and 140 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL	:	= 25 mg/kg
LOAEL	:	= 70 mg/kg
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1989
GLP	:	yes
Test substance	:	other TS
Method	:	Groups of 20M and 20F S-D rats were administered 0, 25, 70 or 140 mg PNP/kg daily in distilled water for 13 weeks by gavage at a constant volume of 10 ml/kg. Dose levels were verified by spectrophotometric analysis. Mortality checks and signs of intoxication were made twice daily, and detailed clinical signs, individual body weights and food consumption recorded weekly. Pre and post study ophthalmoscopic examinations were also conducted on all animals available. At weeks 7 and 14 extensive hematology (RBC, RETIC, HGB, HCT, PLATELET, WBC, differential Leukocytes, and cell morphology) and serum chemistry (GLU, BUN, CREAT, AST, ALT, GGT, T PROT., ALBU, GLOB, CA, T BILI, PHOS, NA, POTAS, CL) parameters were conducted on blood

samples from 10 animals/sex/group. No urinalysis was performed. At termination brain, liver, kidney, spleen and testes with epididymides were weighed for all survivors and a full necropsy performed. A full set of approx. 40 tissues and organs (including gonads) were collected from all surviving animals and sections were examined microscopically from these tissues for the control and high dose animals. Microscopic examination of tissues was also performed on tissues of premature deaths exhibiting gross autopsy findings. Temperature, lighting and humidity were controlled throughout the study. Body weights and weight gains, food consumption, hematology and clinical chemistry parameters and organ weights (absolute and relative) were initially analyzed using Levine's test of homogeneity of variances. If nonhomogeneous, data were transformed and then analyzed via ANOVA ($p<0.05$). Dunnett's t-test (2-tail, $p<0.05$) was used to compare treated and control groups. Cumulative survival was assessed using the National Cancer Institute statistical package and analyzed for trend.

Result :

Early deaths were seen in groups of male and female rats given 70 and 140 mg/kg/d PNP. Total premature deaths observed in 0, 25, 70 and 140 mg/kg males were 0,0,1, 15, respectively; for females - 0,1,1,6, respectively; Several of these premature deaths (1-70 mg/kg male, 2 @ 140 mg/kg male, 3 @ 140 mg/kg female) died shortly after bleeding at wk 7, which likely exacerbated deaths, while 1 HD male was found to have died from gavage error. All other deaths at 70 mg/kg and 140 mg/kg were considered related to PNP exposure as they exhibited significant clinical signs of toxicity (pale appearance, languid behavior, prostration, wheezing and dyspnea), died shortly after dosing and exhibited moderate to severe congestive liver, kidney, lungs and adrenal cortex pathology (which correlated with necropsy findings) after microscopic examination; The presence of clinical signs of toxicity and absence of specific histopathological changes in these premature deaths suggests a relationship to acute pharmacologic/toxicologic effect. The single premature death observed in the LD female group was not considered treatment-related as there were no clinical signs observed, it did not die shortly after dosing (was found dead overnight) and had little in the way of organ congestion. Significant increases were observed in segmented neutrophils and absolute monocytes and eosinophil counts, as well as polychromasia of erythrocytes in 140 mg/kg animals of both sexes; these findings were considered of no toxicological significance. No treatment-related effects were observed in clinical signs, body weights, food consumption, ophthalmoscopic examination, organ weights or histopathology of survivors. Specifically, no effects were observed on gonads in this study. A NOEL was established as 25 mg/kg/d.

Test substance : Purity of 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.02.2004 (20)

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	4 weeks
Frequency of treatm.	:	6 hr/d, 5 days/week
Post exposure period	:	none
Doses	:	0, 1, 5, and 30 mg/m3
Control group	:	yes
NOAEL	:	= 5 mg/m³
LOAEL	:	= 30 mg/m³
Method	:	OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year	:	
GLP	:	yes
Test substance	:	other TS

Method :

Groups of 15 male and 15 females S-D rats were exposed to target concentrations of 0, 1, 5 or 30 mg/m3 of PNP dust via whole body exposure in 1000 L glass and stainless steel chambers. Chamber concentrations were generated via use of a Wright dust feed and determined 3X daily by gravimetric analysis. Particle size determinations were measured weekly. Food and water were available ad libitum at all times other than during exposure. Temperature and humidity, as well as light:dark cycle were controlled. Animals were observed twice daily for mortality and signs of toxicity. Each animal was carfully examined and weighed weekly. Hemoglobin and methemoglobin concentrations were determined by orbital sinus during week 2. Ophthalmic exams were conducted just prior to terminal sacrifice on all animals. The following hematology (RBC, HCT, HGB,PLATELETS, RBC morph, and total and differential leukocyte counts, and clotting time) and blood chemistry (ALT, AST, BUN, TOT BILI, GLU, LD, CHOL, NA, POTAS, CA, CL, PROT, ALBU, GLOB) were evaluated after 4 weeks. No urinalysis was performed. Complete necropsies were conducted on all animals on test. The following organ weights were recorded: lungs, liver, kidneys, brain, heart, adrenals, spleen and testes with epididymides. Thymus wt was not recorded. Histopathological examinations were conducted on approximately 40 tissues and organs, and all gross lesions observed at necropsy, on all high dose and control animals. Clinical pathology, hematology, weekly body weights and weight gains, organ weights and weight ratios of control groups were compared statistically to treated groups of the same sex. Box test was used to determine homogeneity of variances followed by a 1-way classification by ANOVA if variances were homogeneous or use of rank transformation if nonhomogeneous. If found significant ($p<0.05$) Dunnett's t-test was used to compare groups ($p<0.05$).

Result :

Mean gravimetric chamber concentrations were 1.09, 5.27, and 29.2 mg/m3. MMD ranged from 5.4-6.9 u. Prestudy analysis indicated that the PNP dust was homogeneously distributed in the stainless steel chamber. No deaths occurred during the study. Except for dose-related yellow staining attributed to

test material, no abnormal physical observations were noted. Ophthalmoscopic examinations revealed 11 cases of diffuse anterior capsular cataracts only in HD males and females. Corneal keratitis sicca (inflammation and drying of the cornea and conjuctiva) was noted in 3 HD animals. Periodic changes in body weights were seen inconsistently and in opposite directions for each sex and thus not considered tretment-related. No consistent, dose-related effect was noted in METH values, while some very slight changes in HGB and HCT were seen in HD males. The relationship of these effects to PNP treatment is unclear. No treatment-related effects were seen in other hematologic or clinical chemistry parameters. No gross or microscopic pathological effects or organ weight changes were noted that were attributed to PNP. No effects on the gonads was observed. A NOEL was established as 5 mg/m3.

Test substance : Purity of 99 %.
Reliability : (1) valid without restriction
29.02.2004 (18)

Type :
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 4 weeks
Frequency of treatm. : once daily for the entire test period
Post exposure period : none
Doses : 0, 1, 10, 50, and 100 mg/kg
Control group : yes, concurrent vehicle
NOAEL : = 50 mg/kg
LOAEL : = 100 mg/kg
Method : other
Year : 1989
GLP : yes
Test substance : other TS

Method : Groups of 5 male and 5 female S-D rats were administered PNP in distilled water by gavage at doses of 0, 1, 10, 50 and 100 mg/kg at a constant volume of 10 ml/kg. Daily clinical signs were recorded and individual body weights and food consumption were taken weekly for all animals. Hematological (HGB, HCT, RBC, TOT /DIFF LEUKO, MET HGB) and clinical pathological (BUN, GLU, CREAT, ALT, ATS, T PROT, ALBU, GLOB, T BILI, PHOS, NA, K, CL) parameters were measured prior to study termination after 4 weeks. Gross necropsy examinations were conducted at the terminal sacrifice and brain, liver, kidneys, spleen and testes with epididymides were trimmed and weighed. Collected tissues (approx. 40/animal) were preserved and gross lesions, kidneys, livers and spleen were prepared from all animals and examined microscopically. Dosing solutions were analyzed by spectrophotometric means for stablity and concentration.

Result :

Analysis of dosing solutions indicated stability and accuracy. One female rat at the 100 mg/kg dose level died shortly after bleeding followed by dosing and is likely

treatment-related. Mean body weights and food consumption in treated groups were comparable to control values. No changes were observed in hematology or clinical chemistry values between treated and control groups. No clinical signs of toxicity were observed in survivors. Organ weights, necropsy findings and microscopic examination of treated rats were similar to controls.

Test substance :

p-Nitrophenol (CASNO 100-02-7), purity 99.1%

Conclusion :

This study was a range-finding study to set dose levels for study no. HL-88-372. As such, no statistical treatment of data was ascertained.

Reliability : (2) valid with restrictions
29.02.2004 (19)

Type	:	Chronic
Species	:	mouse
Sex	:	male/female
Strain	:	Swiss Webster
Route of admin.	:	dermal
Exposure period	:	18 months
Frequency of treatm.	:	3 days per week
Post exposure period	:	none
Doses	:	40, 80 or 160 mg/kg in acetone
Control group	:	yes, concurrent vehicle
NOAEL	:	= 160 mg/kg bw

Method :

Sixty Swiss-Webster mice of each sex received 0, 40, 80, or 160 mg/kg p-nitrophenol in 100 microliters acetone applied directly to the interscapular skin three times per week (Monday, Wednesday, and Friday; excluding holidays) for 78 weeks. Fur in the area of skin receiving the dose application was clipped weekly. Doses selected for the 18-month studies were based on the survival and histopathologic lesions from 13-week studies conducted at the Gulf South Research Institute. (unpublished data). The study conduct followed the NTP statement of work.

Dose analyses of p-nitrophenol in acetone were performed at approximately 2-month intervals by the study laboratory using flame-ionization gas chromatography with n-undecanol as internal standard. Dose formulations were within 10% of the desired level during the entire study

Mice were examined twice daily for mortality, changes in appearance or behavior, and signs of toxicologic or pharmacologic effects. Clinical findings were recorded weekly for the first 13 weeks, then at 4-week intervals thereafter until the end o f the study. Body weights were recorded weekly for the first 12 weeks, then every 4 weeks until the end of the study. Complete necropsies were performed on all mice. During necropsy all organs and tissues were examined for gross lesions. Complete histopathologic examination was performed on all mice. Tissues selected for microscopic examination were preserved in 10% neutral buffered formalin. To prepare the tissue for microscopic examination, the preserved tissue was embedded in paraffin, sectioned 4 to 6 pm thick, and stained with hematoxylin and eosin. The NTP complete list of tissues was examined microscopically.

Result	:	Survival of dosed male and female mice was similar to that of the controls. (Survival of 40 mg/kg males was significantly lower than that of controls but this was not considered to be related to chemical administration) There were relatively few deaths during the first 60 weeks o f the study, and thereafter, survival began to decrease abruptly for all dosed and control groups. Body weights of dosed mice were similar to controls throughout the study. No statistically significant or biologically noteworthy changes occurred in the incidences of nonneoplastic lesions at any site. There we no compound-related increases in any neoplasm. A full description of the results is available in NTP TR 417 which can be found on the NTP website at http://ntp-server.niehs.nih.gov/htdocs/LT-Studies/TR417.html
Test substance	:	p-Nitrophenol CASNO 100-02-7 > 97% purity
Conclusion	:	Under the conditions of these 18-month dermal studies there was no evidence of carcinogenic activity or target organ effects other than the skin in male or female Swiss-Webster mice receiving 40, 80, or 160 mg/kg p-nitrophenol.
Reliability	:	(1) valid without restriction NTP Statement of Work study under GLP's, peer-reviewed and publically available.

29.02.2004 (15)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium strains TA100, TA98, TA1535 and TA1537
Test concentration	:	0, 10, 33, 100, 166, 333, 666, 1000 ug/plate
Cycotoxic concentr.	:	1000 ug/plate (TA100)
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	1983
GLP	:	yes
Test substance	:	other TS
Method	:	Methodology used by NTP based on Ames test plate incorporation assay and consistent with OECD 471. All tests were run in duplicate and three plates were assayed at each dosage for each run both with and without metabolic activation; S9 obtained from male S-D rats injected with Arochlor 1254 (500 mg/ml) five days before they were killed; all tester strains obtained originally from B. Ames; the high dose was designed to produce toxicity (reduced background lawn or solubility limits; sterile DSMO was used as the solvent; negative (solvent) and positive controls (2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium azide and 9-aminoacridine) used were appropriate to detect mutagenicity with or without metabolic activation in each of the 4 tester strains used. A positive response was detected

if a reproducible, dose related increase (>2X) was seen in revertant colonies according to a model described by Margolin et al 1981.

Remark :

This result is supported by a secondary tier Drosophila Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program National Toxicology Program (NTP). 1994. Toxicology and carcinogenesis studies of p-nitrophenol in Swiss-webster mice (dermal studies). Technical Report Series No. 417, US Dept. HHS, PHS, National Institutes of Health.

This result is also supported by a 1990 report that PNP elicited no mutagenic activity when tested in a CHO-HGPRT forward mutation assay in mammalian cells. Oberly, TJ, Rexroat, MA, Beusey, BJ, Richardson, KK, Michaelis, KC. 1990. An evaluation of the CHO/HGPRT mutation assay involving suspension culture and soft agar cloning: Results for 33 chemicals. Environ Mol Mutagen 16(4):260-271.

Result :

No increase in revertants were observed with or without metabolic activation in any of the 4 tester strains.

Test substance : Purity = 99%.

Reliability : (1) valid without restriction
While no statistical methods were used, none were needed to visually inspect and render a conclusion of no increases observed in revertants in any tester strain; further, these findings are consistent with other literature citations using similar methodology

Flag : Critical study for SIDS endpoint

29.02.2004 (10)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary cell culture
Test concentration : 100 to 2500 ug/ml
Cycotoxic concentr. : not stated
Metabolic activation : with and without
Result : positive
Method : other
Year :
GLP : yes
Test substance : other TS

Method : Study performed under auspices of US NTP program. Doses were based on a preliminary test of cell survival 24 hr after treatment. Cells were collected 10.5 h after treatment by mitotic shaking-off. Slides stained with Giemsa and coded. 100 cells were scored from each of the 3 highest dose groups having sufficient metaphases for analysis (cells with 19-23 metaphases chosen); Positive control groups treated with triethylenemelamine, mitomycin C or Cyclophosphamide), solvent control also used.. Aberrations were typed and recorded separately but analyzed grouped into categories of simple (breaks and terminal deletions), complex (rearrangements and exchanges) and other (i.e pulverized chromosomes). Gaps and endoreduplications were recorded but not included in totals. Aberrations in polyploid cells were not scored. Linear regression of the percentage of cells

with aberrations vs. the log-dose was used as the test for trend. A binomial sampling assumption was used and data were analyzed according to the method of Margolin et al Environ Mutag 8:183 (1981). P values were adjusted by Dunnett's method to take multiple dose comparisons into account.

Remark :

In a concurrent study PNP was negative for SCE induction up to doses that caused severe cell cycle delay (25 ug/ml -S9; 1700 ug/ml +S9). National Toxicology Program (NTP). 1994. Toxicology and carcinogenesis studies of p-nitrophenol in Swiss-webster mice (dermal studies). Technical Report Series No. 417, US Dept. HHS, PHS, National Institutes of Health.

Result :

No treatment-related increase in the frequency of structural aberration were noted up to severe cytotoxic levels (>750 ug/ml -S9; Reproducible , dose-related and significant increases in cells with structural chromosomal aberrations were seen at test levels of 1500 to 2000 ug/ml +S9 that induced severe cell cycle delay.

Test substance : Purity of 99 %.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.02.2004 (5)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : Two generation study
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : F0: males - 113 doses; females - 118 doses; F1: males - 190 doses; females - 180 doses
Frequency of treatm. : once per day, 5 days per week
Premating exposure period
Male : 140 days (100 doses)
Female : 140 days (100 doses)
Duration of test : Through prebreeding, breeding ,gestation, lactation and development through two full generations (1 litter per generation), F2 pups observed through 30 days postweaning.
No. of generation studies :
Doses : 50, 100, and 250 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL parental : 250 mg/kg bw
NOAEL F1 offspring : 250 mg/kg bw
NOAEL F2 offspring : 250 mg/kg bw
Method : other
Year : 1985

GLP : yes
Test substance : other TS

Method : 5-Week old Charles River CD rats began treatment, consisting of 120 female and 60 male rats housed in wire mesh caging. Humidity, temperature and light:dark cycle were controled throughout the study. Water and food were available ad libitum. After random assignment, each of the five test groups began the study (Fo generation) with 24 females and 12 male rats per group. All rats were clipped free of hair along the dorsal body line and reshaved as necessary to allow good dermal contact with the test agent. Dosing periods were lengthened over the periods recommended by EPA guidelines to compensate for a 5-day per week dosing period in this study. Test agents were applied dermally using appropriate-sized syringes, once daily, 5 days /week. Animals were individually weighed at the beginning of each study and dose levels adjusted. F0 animals were treated for the first 140 days of the study (100 applications each). Thereafter, one half of the females in each group were paired with corresponding males until either positive mating was achieved (presence of sperm plug and confirmed by vaginal smear) or it became evident that the pair would not mate. In the latter cases additional cohousing occurred until it became apparent that no further mating would ensue. After successful mating, males and females were separated; F0 males were held until all mating ceased, at which time they were sacrificed and testes, epididymis and skin sections were taken for histopathologic evaluation. Dosing of F0 females continued through the breeding, gestation and lactation periods. Females dosed during gestation were based on the last premating weight. Approximately 21 days after birth, the F1 generation was weaned and F0 females sacrified with their ovaries, uterus and skin sections taken for histopathologic examination. 13 males and 26 females from the F1 generation were randomly selected for continued dosing and breeding in a manner similar to the F0 generation. Application of test materials continued over the next 168 days (120 applications each). Following this period, the F1 rats were mated in a procedure corresponding to the mating of the F0 parental animals. Five males and 5 female pups from the F1 generation were selected at weaning for complete necropsy exam. An additional 5 F2 males and 5 F2 females from each group were randomly selected and retained in wire cages for 30 days after weaning. Dosing of all F1 rats continued throughout breeding, gestation, lacatation and until 30 days after all F2 rats had been weaned. Thereafter, all F1 rats and remaining F2 rats were submitted for complete necropsy. All animals dying spontaneously during the course of the study were submitted for necropsy. All rats which underwent necropsy were subjected to histopathological assessment of the following tissues and organs: (brain, spinal cord, eye, salivary gland, heart, thymus, thyroid, lungs, bronchi, esophagus, stomach, small intestine, large intestine, pancreas, adrenal glands, kidneys, liver, testes, epididymis, urinary bladder, male accessary glands, ovaries, corpus uteri, cervix uteri,

spleen, lymph nodes, sernum, femur, skeletal muscle, mammary gland, treated skin and untreated skin. Organ weights were recorded for scheduled sacrifies from F1 and F2 animals: liver, kidneys, heart, gonads (F0 males also), and brain.

Observations for toxic signs, breeding and nesting behavior were recorded daily for all animals. Weights of all dosed rats were recorded weekly. Breeding and litter observations included: litter size, individual pup weights and viability at birth and on days 4, 7, 14, and at weaning. The following indices were calculated to assess reproductive success: fertility (no. of pregnancies/no. mated) gestation (% of pregnancies resulting in birth of live litters), viability (pups surviving at least to day 4 of life) and lactation (pups surviving at least to day 21 of life). Group-wise statistical ($p < 0.05$) comparisons were made of body weights, absolute and relative organ weights.

The High dose (250 mg/kg/d) was selected based on a range-find study indicating this level to be 1/4 LD50 dermally, and would allow sufficient survival; both an ethanol vehicle (used at 500 mg/ml) control group (0.5 ml/kg/d) and a saline control group (0.5 ml/kg/d) were also evaluated concomittantly. Multigeneration study methodology was modified (dosing took place 5 d/wk rather than 7 d/wk) from test guidelines recommended in TFX Collins Handbook on Teratology, Vol. IV, Chapter 7: Multigeneration Reproduction Studies. 1978.

Result :

All F0 and F1 rats dosed dermally with PNP or ethanol exhibited a pattern of dermal irritation consisting of varying degrees of erythema, scaling, scabbing and cracking ; some degree of dose-response was noted in PNP-treated groups. No treatment-related mortality was observed in either the F0 or F1 parental generation, and no effects of treatment were noted in body weights in these groups. No evidence of effects in mating, pregnancy, behavior,and growth were found in parents or subsequent F1 and F2 generations.All group-wise comparison of organ weights, including gonads, were unremarkable. No evidence of histopathologic alterations was seen in any tissue examined, including the gonads.

Test substance : Purity of test substance used - 99.1%

Reliability : (1) valid without restriction
Study sufficiently adequate to be accepted to fulfill US EPA pesticide reregistration requirement for reproductive toxicity endpoint.

Flag : Critical study for SIDS endpoint

29.02.2004 (1)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage

Exposure period	:	gd 6 to 16
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	1.4, 13.8 or 27.6 mg/kg-day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 13.8 mg/kg bw
NOAEL teratogen.	:	= 27.6 mg/kg bw
Result	:	not a developental toxin in the rat
Method	:	
Year	:	
GLP	:	no data
Test substance	:	

Method :

Test material, in propylene glycol solution, was administered by gavage to groups of 20 pre-mated female Sprague-Dawley rats at dose levels of 0, 1.4, 13.8 or 27.6 mg/kg-day from days 6 through 16 of gestation. A positive control group (aspirin, 250 mg/kg-day) was included in this study. Rats were sacrificed prior to delivery and the products of conception were examined for viability, morphology and other standard fetal parameters.

Result :

Decreased maternal body weight (12%) and body weight gain (45%) were observed during the dosing period at the high-dose level of 27.6 mg/kg-day. Treatment-related effects on mortality, clinical signs, food consumption or cesarean parameters were not reported. Food consumption was not measured.
Based on decreased body weight and body weight gain the maternal LOEL is judged to be 27.6 mg/kg-day. The maternal NOEL was found to be 13.8 mg/kg/day. The developmental NOEL was found to be 27.6 mg/kg-day and a developmental LOAEL was not found.

Treatment-related developmental toxicity was not observed; however, the small number of litters (10) available for examination at the high dose level and the lack of some experimental details in the report reduce reliability of the results. A developmental NOEL of 27.6 mg/kg-day can be assigned. A developmental LOAEL was not established in the study.

Test substance :

p-Nitrophenol (CASNO 100-02-7), purity 99.1%

Conclusion :

It is concluded that the test material did not demonstrate any developmental toxicity even at doses associated with clear maternal toxicity.

Reliability : (2) valid with restrictions

Although the number of litters was sub-optimal, and some experimental details are missing, the lack of any adverse effects on developmental parameters in animals where maternal weigh-loss was reported during administration of test material is a strong indication that the test material is not a developmental toxin. The study is assigned a reliability score of 2 because of it lacks details.

Flag : Critical study for SIDS endpoint

29.02.2004 (2)

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